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LIVER FUNCTION TESTS

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The clinical laboratory and laboratory methods are developing in increasing importance as aids in the diagnosis and treatment of disease. Among the newer acquisitions of the clinical laboratory are the so-called functional tests, and their importance has grown so that they occupy no small part of the time of the average clinical laboratory. In a measure this condition is a triumph for physiology because it implies that the clinician has finally recognized that this least appreciated of the sciences of medicine represents a standard which he can well afford to use. It also implies that at least in many instances the pathologic condition is but a deviation from the normal. While this augurs very well for the scientific advance of modern medicine, it must be confessed that many of the so-called functional tests suggested and devised for testing the functional capacity of the various organs are as empiric in fact as any one of the numerous drugs which fill the pharmacopeia. This condition is due to some extent to the physiologist's failure to realize the rapid progress of clinical medicine, and the awakened desire of the clinician to enlarge the field of diagnostic medicine beyond its present scope, and to diagnose disease earlier before the development of the later signs, considered at present essential to diagnosis, and thus enhance the possibility of either preventing the disease or treating it in its incipiency. It is also due to the clinician's failure to realize that true growth can be based only on facts, and that an imaginary conception supported by inaccurate data can only retard the advance of scientific medicine.

It would seem desirable that a certain standard or criteria be established for the real functional test of an organ. Such a test presupposes a certain amount of knowledge of the function of the organ to be

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tested, some estimation of its normal functional capacity and a standard pathologic lesion or clinical syndrome which specifically affects the organ. It is difficult to understand how a functional test can be used for an organ unless the function of the organ is known and the test applied specifically to such a known function. Furthermore, the normal capacity of the organ for that specific function should be capable of being estimated. Finally, it is hardly possible to determine the efficacy of a functional test unless it can be standardized by means of a definite pathologic condition known specifically to involve the organ in question.

When such criteria are applied to the tests suggested to estimate the functions of the liver, it is readily seen that few can be called true functional tests. Many of the tests were devised to measure a supposed function of the liver; some were devised for functions which were wholly imaginary, and some involved physiologic phenomena which were not specific activities of the liver. Many of the data presented as substantiating the value of various of these tests are vitiated by a certain vicious circle of reasoning. The test in question was applied to a certain group of cases, none of which had been proved either clinically or at necropsy to be disease of the liver; when the test was positive it was considered a good test of hepatic function and to be disease of the liver; the condition was designated as hepatic insufficiency. In such instances neither the measure nor the entity to be measured are known.

We have studied the physiology of the liver for several years. Although our primary purpose has been to obtain more accurate knowledge concerning the function of this great organ, we recognized that if the patient was to benefit from any knowledge thus gained it would be necessary to bear in mind the possible application of the data obtained to clinical medicine. We have constantly considered the facts as they presented themselves in relation to the diagnosis and treatment of disease of the liver. We thus accumulated a large amount of data bearing on the tests that have been devised for measuring the functional capacity of the liver. These data, with the conclusions based on them, we wish to present here.

Previous work on functional tests of the liver will not be reviewed extensively since this has recently been done by Greene, Snell and Walters;[1] nor is it necessary to give the details of the technic of the various tests except in the instances in which we have found it necessary to alter them. Such details can best be obtained from the original sources. Furthermore, the clinical employment of these tests will not be

1. Greene, C. H.; Snell, A. M., and Walters, Waltman: Diseases of the Liver: I. Survey of Tests for Hepatic Function, Arch. Int. Med. **36**:248-272, 1925.

discussed, since Rowntree and his associates are making a comprehensive study of the problem. We shall present the results of an experimental review of the most suggestive tests in relation to the known functions of the liver. Our conclusions are based on the results of several hundred experiments.

METHOD OF INVESTIGATION

Experiments were performed on normal animals, on animals in which an Eck fistula had been made, on animals in which the hepatic tissue had been permanently greatly reduced and on animals in which the liver had been totally removed. This wide range of fairly standard hepatic conditions gave ample opportunity for a thorough investigation of each test.

Our first study was on the effect of total removal of the liver.[2] This study has been productive of important data, but mainly of physiologic importance. However, the results furnished us with a certain physiologic standard of criteria whereby we could judge the rationale and efficacy of a test. Furthermore, whenever feasible the test was carried out on an animal from which the liver had been totally removed. These experiments were of particular value in eliminating supposed functional tests of the liver which give positive results even if the organ is absent.

The ideal method of determining experimentally the value of any functional test would be to employ it in an animal with a pathologic condition identical with that found in man. This ideal condition has rarely been approached with regard to any organ and certainly not with the liver. While a certain degree of cirrhosis of the liver can be produced experimentally by several methods, the method of production often makes it impossible to employ functional tests with profit. In many of the studies dealing with hepatic damage, and the resulting changes in function, the more or less specific hepatic poisons, as chloroform and phosphorus, have been used. While such studies have undoubtedly afforded considerable valuable information, it must be recognized that such experiments were also complicated by the action of the poisons on other organs, as well as by the large amount of damaged hepatic tissue.[3] With reference to the latter, it may be said that the autolysis of only a small percentage of the total amount of hepatic tissue in the abdominal cavity is sufficient to produce a rapidly fatal outcome.

The high regenerative power of the liver offers the greatest difficulty in the experimental production of chronic hepatic insufficiency.

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2. Mann, F. C.: Studies on the Physiology of the Liver. I. Technic and General Effects of Removal, Am. J. M. Sc. **161**:37-42, 1921.

3. Williamson, C. S., and Mann, F. C.: Studies on the Physiology of the Liver. V. The Hepatic Factor in Chloroform and Phosphorus Poisoning, Am. J. Physiol. **65**:267-276, 1923.

It has the capacity to recover from the effects of many and severe organic insults, such as trauma, action of the hepatic poisons and also surgical removal.[4] We have attempted to reduce its functional capacity by several methods, but found it impossible even approximately to standardize any of them except surgical removal. We have not found it possible to reduce the liver tissue of the normal dog permanently. In the dog the different lobes of the liver stand out separately, so that it is anatomically possible to remove most of the organ lobe by lobe. While there is considerable variation in the total amount of liver to total body weight and also in the relative size of the various lobes, it is possible, with experience, to estimate approximately the relative amount of hepatic tissue removed and the total amount left in the animal. While it is possible to remove or leave any lobe or combination of lobes, it is necessary to leave whole lobes; partial removal of a lobe is usually fatal because of hemorrhage or the destruction of the vascular radicles to the portion remaining. The maximal amount of hepatic tissue that can safely be removed from a dog, because of anatomic conditions, is limited to certain combinations of lobes, which rarely exceeds 70 per cent of the total amount of hepatic tissue. If as much of the liver is removed as it is anatomically possible to remove from a normal animal, the remaining tissue will increase, and in a few weeks will have returned approximately to its preoperative level. As new lobes do not form, and the return to normal size is by an increase in the remaining lobes, it is impossible to remove a significant portion of the regenerated liver. This great regenerative power of the liver, together with the anatomic limitation of removal, prevents the permanent reduction of hepatic tissue in the normal animal.

When an Eck fistula has been made, characteristic atrophy of the liver occurs, usually well marked at the end of two or three months. The atrophy is progressive, and while an animal with an Eck fistula usually loses some weight, the atrophy of the liver is out of proportion to the loss of general weight of the body. For instance, an Eck fistula was made in an animal weighing 18 Kg. Nineteen months later it weighed 14 Kg., but its liver weighed only 145 Gm. The liver was reduced to at most one-fourth its weight before the operation.

We found that the liver's ability to recover following its partial removal depends for the most part on an intact portal circulation.[5] In an animal in which the portal circulation has been diverted by an Eck fistula some few weeks before a portion of the liver has been removed,

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4. Ponfick, E.: Experimentelle Beiträge zur Pathologie der Leber, Arch. f. path. Anat., Supp. **38**:81-117, 1895.

5. Mann, F. C., and Magath, T. B.: The Production of Chronic Liver Insufficiency, J. Physiol. **59**:485, 1922.

usually there will be very slight, if any, regeneration of the remaining portion. Occasionally, especially if a very large part of the liver is removed at one time, there will be a noticeable increase in the size of the remaining portion, but never approaching the amount of recovery in the normal animal. The finding that the liver's ability to regenerate depends on an intact portal circulation has enabled us permanently to reduce the amount of hepatic lesion. Our routine method of accomplishing this was to make an Eck fistula and after from a few weeks to several months to remove various amounts of the liver surgically. This procedure made it possible to decrease the amount of hepatic tissue to a small percentage of the normal amount and maintain the animal in this condition for many months.

It was found possible to estimate only approximately the amount of functional hepatic tissue of any animal. In removing a portion of the liver of an animal with an Eck fistula, the amount of tissue remaining was estimated in comparison with the amount removed, and, as the latter was weighed, an estimate in grams and percentage was possible. Furthermore, an estimate of the amount of total atrophy of the liver that had occurred subsequent to the diversion of the portal circulation which was approximately correct, could be made by comparing the weight of the removed tissue with the average weight of the same lobe of liver from an animal of the same weight. By histologic examination it was then possible to estimate the percentage of hepatic cells which appeared sufficiently normal to be considered active. Finally, the weight of the hepatic tissue obtained at necropsy furnished the exact amount, in relation to the amount removed. These data were sufficient to enable us to make approximate estimations of the amount of functional hepatic tissue the animal possessed at the time of any particular test in relation to the amount possessed at the beginning of the experiment. We were always conservative in making an estimation, and believe that in many instances the hepatic function was much less than that estimated.

As the diversion of the portal circulation was a necessary stage in our method of permanently reducing the size of the liver, we were forced to study the reaction of the animal with an Eck fistula to the tests. In general it may be said that such studies, with a few exceptions, afforded little of value, because this procedure does not effect a sufficient decrease of the functional capacity of the liver.

Adequate control observations were made on normal dogs. In many instances the tests were carried out on the normal animal; then an Eck fistula was made and the test repeated, and finally the liver was partially removed surgically and the test repeated at different intervals for several months. Such studies have been carried out on certain animals for more than two years.

It is a well known fact that the animal with an Eck fistula often cannot be kept in good condition, and occasionally does very poorly regardless of the care and attention bestowed on it. However, a diet composed mainly of carbohydrate and mild protein appears to be the most suitable. After employing various diets, we found that one composed mainly of milk and commercial corn syrup gave the best results. The judicious use of such a diet will maintain an animal with Eck fistula, or one with greatly reduced hepatic tissue, in a normal appearing condition for years.

TESTS OF HEPATC FUNCTION DEPENDING ON THE SECRETION OF BILE

As the liver performs so many and such varied functions in which the exchange of component constituents is between the hepatic cell and blood or lymph stream, and since some of the products thus elaborated can be considered as products of internal secretion, it seems best to consider the secretion of bile as the external secretory function of the liver. A study of the external secretion is handicapped by the fact that the secretion is poured into the intestine and is not readily accessible for observation. This anatomic handicap is a very real one in determining the physiologic factors involved in the secretion of bile, although, because of the varied activity of the liver it may not greatly deter functional tests. It is questionable whether a study of the bile alone will present a complete estimate of the hepatic capacity for functional activity. In this connection it might be well to point out that even the most important reported studies of the various competent investigators on the factors concerned in the formation and secretion of bile in animals with biliary fistula contain an astonishing amount of contradictory results and conclusions.

In experimental work it has been possible to study bile secretion by draining it to the exterior, but in the study of man only three methods have been available for observing such activity; these are: a study of the hepatic products in the stool, a study of the duodenal contents by duodenal drainage and a study of the rate of disappearance from the blood stream of substances specifically excreted by the liver. It is readily seen that any of these methods can give only approximate results. All methods have serious disadvantages, the last, although only an indirect approach, is probably the most satisfactory. The bile is composed of several constituents, of which up to the present only three have been considered sufficiently specific to warrant their investigation as applicable to tests of hepatic function. These are cholesterol, bile salts and bilirubin.

While the cholesterol is undoubtedly one of the most important constituents of the bile not only physiologically but pathologically, and

while it must be of great importance in the bodily economy, its study does not at present seem to offer much opportunity of measuring hepatic function. Accurate knowledge concerning its origin, rate of formation, function and relation to the liver are wanting. We have not observed any demonstrable quantitative changes in the cholesterol of the blood following total removal of the liver.[6]

In many respects the bile salts would appear to offer an excellent means for developing a test of hepatic function, since they are probably the most active agent in producing the symptoms and physiologic and pathologic changes found in cases of obstructive jaundice. It is strongly indicated

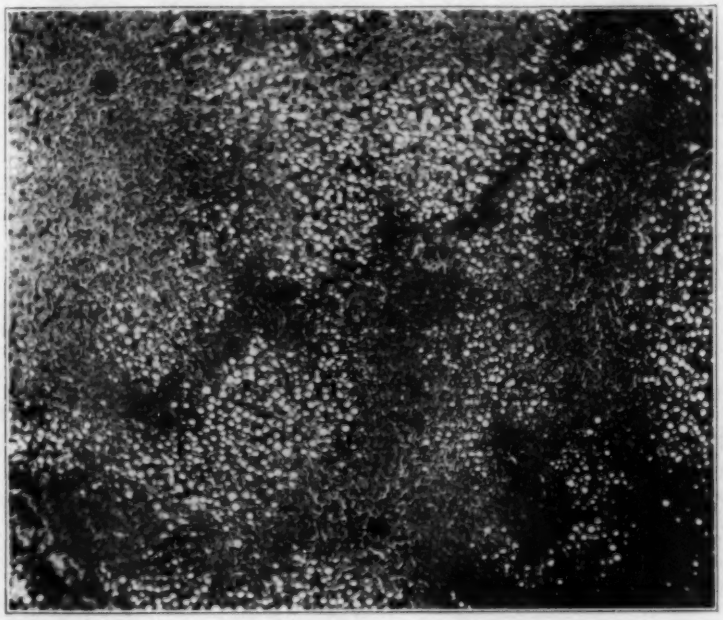

Fig. 1.—Section of liver removed forty days after Eck's fistula was made. At this time the liver was partially removed. It was estimated that about 25 per cent of the normal weight of the liver remained after operation. Subsequent explorations revealed little hypertrophy, and the animal is alive and in fair condition eighteen months after the operation; × 60.

that they are made by the liver, although this question is not settled. However, the possibility of making the bile salts a basis of a test of hepatic function remains only speculative, as such an investigation awaits the development of accurate methods of estimating the bile salts in the blood. Even if such an accurate method does not give a satisfactory test of hepatic function, it should give an estimate of the damage done in cases of jaundice, particularly of the obstructive type.

6. Mann, F. C.: Modified Physiologic Processes Following Total Removal of the Liver, J. A. M. A. **85**:1472-1475, 1925.

Jaundice was the first clinical sign observed of hepatic insufficiency, and has always been considered the most important. There is no question that the liver is always affected in a condition of jaundice, yet it is not possible to tell by a study of jaundice alone whether it is directly or indirectly involved, and the degree of involvement. With the development of the van den Bergh test [7] and to a lesser degree the icteric index [8] for estimating the bilirubin in the plasma, a great advance was made in the study of jaundice. It is unnecessary to discuss here the van den Bergh test as a clinical test, not only because of the large amount of data that have been presented concerning it, but also because its value as a clinical test has been fully established.[9] We shall present rather some observations having a bearing on this test which could be made only in connection with experimental work.

However valuable the estimation of the amount of bilirubin in the plasma may be as a clinical indicator whereby the clinician may diagnose a lesion or give a prognosis, or the surgeon may determine when to operate and when not to operate, it will not serve as a simple test of hepatic function. Other factors almost as important as the hepatic are involved in the accumulation of bile pigment in the blood. Although there is proof that the liver does make bile pigment,[10] more of this pigment is made by the spleen and bone marrow than by the liver.[11] So that, as a part of the process of jaundice and in relation to the serum bilirubin value, the extrahepatic sources of bilirubin must also be considered. It is also definitely proved that bilirubin is made from hemoglobin;[12] it has not been proved that it is made from other materials. The amount of bilirubin formed and the rate at which it forms depend on several factors, some of which are unknown. We do know, however, that the availability of hemoglobin is one of these factors, although a variable one. This must be considered in the interpretation of the van den Bergh test. The amount of hemoglobin available for making bilirubin depends on factors such as destruction of blood, diet and loss of blood. We have found that the rate at which bilirubin forms is extremely variable and is often influenced by such factors as hemorrhage and anesthesia. It is thus readily seen that the van

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7. Van den Bergh, A. A. H.: La recherche de la bilirubine dans le plasma sanguin par la méthode de la réaction diazoique, Presse méd. **29**:441-443, 1921.

8. Blankenhorn, M. A.: Acholuric Jaundice, Arch. Int. Med. **27**:131-134, 1922.

9. Judd, E. S.: Surgical Procedures in Jaundiced Patients, J. A. M. A. **85**: 88-91, 1925.

10. Mann, F. C.; Sheard, Charles; Bollman, J. L., and Baldes, E. J.: The Liver as a Site of Bilirubin Formation, unpublished data.

11. Mann, F. C.; Sheard, Charles; Bollman, J. L., and Baldes, E. J.: The Site of the Formation of Bilirubin, Am. J. Physiol. **74**:497-510, 1925

12. Mann, F. C.; Sheard, Charles; Bollman, J. L., and Baldes, E. J.: The Formation of Bile Pigment from Hemoglobin, Am. J. Physiol., in press.

den Bergh test cannot be considered wholly from the aspect of the liver or as a test of hepatic function.

The value of the direct and indirect van den Bergh tests as differential diagnostic tests can be determined only by careful and controlled observations on the human being, because we have found that the test in species of different animals differs considerably. For instance, the van den Bergh test when applied to the bilirubin of the dehepatized animal frequently becomes biphasic when the animal becomes jaundiced; we have rarely obtained a definite direct reaction. In some species of animals a direct reaction occurs with the bile obtained from the gallbladder

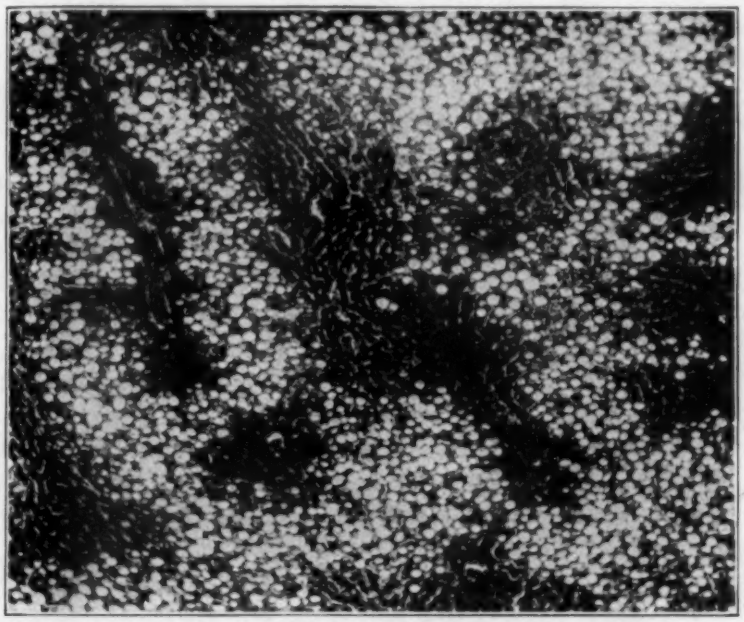

Fig. 2.—Section of liver removed eight months after part of the liver had been removed and twelve months after Eck's fistula had been made. Necropsy a few days after the removal of this specimen showed the weight of liver to be 30 per cent of the normal in animals of this size; × 60.

and only an indirect reaction with the bile obtained from the hepatic ducts direct from the liver. The bile for one species of animals which does not possess a gallbladder never gives a direct reaction. This would appear to be sufficient to prove that the mechanisms of the direct and indirect van den Bergh tests are not simple.

We have noted one finding which would appear to indicate that while the liver has ample reserve for secreting bile pigment it is a function more easily impaired than some of its other functions. When approximately 70 per cent of a normal dog's liver is removed surgically, definite

although transient bilirubinemia occurs which appears to be due simply to a retention of the bilirubin formed extrahepatically. If the same amount of the liver of an animal with an Eck fistula is removed, a more marked and longer continued bilirubinemia occurs than in the normal animal, and occasionally jaundice has been observed.

TESTS OF HEPATIC FUNCTION BASED ON THE RELATION OF THE LIVER TO CARBOHYDRATE METABOLISM

The results of our experiments on the effect of total removal of the liver clearly demonstrated that the liver has a vital function in relation to carbohydrate metabolism.[13] At all times and apparently under all conditions, the liver is constantly regulating the blood sugar level. The concentration of the sugar of the blood is one of the physiologic constants, and one of the functions of the liver is to maintain this concentration within narrow limits under the wide variety of bodily activities. Hyperglycemia, of the more or less permanent type due to loss of the pancreas, and of the transitory type due to asphyxia or drugs, such as epinephrine, are dependent on the liver. The responsibility of the liver as a regulator of the blood sugar level also makes it the logical site of storage of glycogen to be used in maintaining this level and the active agent in making glucose from other materials. Probably the liver is either directly or indirectly affected by the entrance or utilization in the body or loss from the body of all carbohydrate or material from which glucose can be made.

It would seem that a test for such an important function could readily be found, but thus far none has been devised which will even approximately measure the function of the liver in relation to carbohydrate metabolism. There are several reasons for the failure to find a test for this vital function. One of the most important is the fact that while the liver is of vital necessity for the normal process of carbohydrate metabolism, it is only one of several tissues involved in this process. The pancreas and muscles are also specifically concerned in carbohydrate metabolism, and while each of these tissues has its own specific function in relation to this important foodstuff, the process, as a whole, is so orderly that the special rôle of the liver cannot be separated for the purpose of measurement.

We have investigated experimentally three phases of the activity of the liver in relation to carbohydrate metabolism as a possible basis for functional tests, and also studied one of the clinical tests which is supposed to measure the functional capacity of the liver. There are: (1) the blood sugar level, (2) glycogen mobilization, (3) glucose toler-

13. Mann, F. C.: The Liver in Relation to Carbohydrate Metabolism, Tr. Assn. Am. Phys. **40**:362-369, 1925.

ance and (4) levulose tolerance. While the glucose tolerance test has been suggested as a test for hepatic function, it has been employed mainly in relation to the diabetic phase of carbohydrate metabolism. The levulose tolerance test still holds a debatable position as a clinical test for hepatic function.

The blood sugar level of the normal dog under standard laboratory conditions with regard to training for the necessary procedures of obtaining blood samples, the fasting before observation, etc., undergoes only a slight fluctuation from hour to hour and day to day. This gives a fairly uniform standard by which to compare the blood sugar level of animals in which the functional capacity of the liver has been decreased.

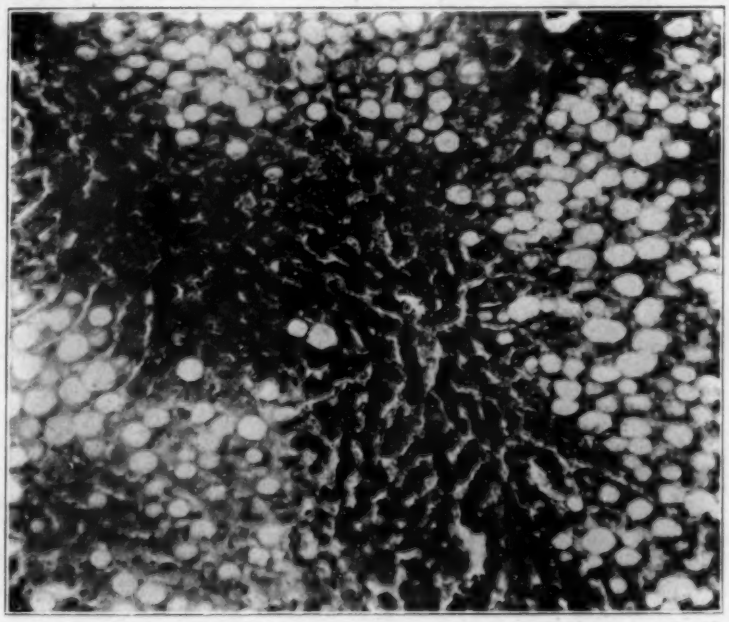

Fig. 3.—Higher magnification of section shown in figure 2; × 120.

The fasting blood sugar level of the animal with Eck fistula is usually slightly lower than that of the normal dog. When part of the liver of an animal with Eck fistula is removed surgically, the blood sugar level is usually slightly decreased, as compared with the level before operation. However, it is possible to detect this decrease in the blood sugar level in the condition of reduced hepatic tissue only by careful control of laboratory conditions. Furthermore, while the level of blood sugar decreased in the animals with reduced hepatic tissue, a level was finally reached at which the blood sugar remained constant, regardless of the further decrease in hepatic tissue. A low fasting level of blood sugar may indicate a failure on the part of the liver, but cannot be used as a

measure of the functional possibilities of the organ, because after all the liver is only a part of the mechanism concerned.

Transitory hyperglycemia, as that which follows general anesthesia, asphyxia and the injection of certain drugs, such as epinephrine, does not occur in dehepatized animals. The liver is essential for its production. While the total glycogen content of the muscles may be as great as that of the liver, only the latter seems to be available to the organism for the purpose of maintaining the blood sugar level.[14] Furthermore, the hyperglycemia that is associated with etherization and operation depends, to a considerable extent, on an intact portal circulation because it does not occur, or occurs only to a slight extent, in animals with an Eck fistula. It would seem that, since the increase in the blood sugar following such processes depends on the mobilization of glycogen by the liver, it would form the basis for a test of hepatic function. However, it must be recalled that changes in the blood sugar level are dependent on many factors, and also that the rate of glycogen mobilization depends on the store of glycogen present, which varies widely within short intervals of time.

The original glucose tolerance test consisted in determining whether glycosuria occurred, and, if so, the amount of glucose excreted by the kidney following the oral administration of a definite amount of sugar. It was readily recognized that the amount excreted in the urine was largely determined by the kidney, and that such tests were often unreliable in indicating the amount of glucose the body could utilize. With the development of accurate and simplified methods of estimating blood sugar, the technic of the test was changed to that of determining the blood sugar level at definite intervals after the oral administration of sugar.

This method also complicates the test by another variable and unmeasurable factor, absorption from the digestive tract. This factor makes it difficult to obtain comparable blood sugar curves in the dog, and, however desirable oral administration may be in the practical application of the test in man, it seemed best to eliminate it in the experimental work. We accordingly administered the glucose intravenously. While the objections can justly be made that such a method is not the normal one for the administration of glucose, that the glucose does not reach the liver in the normal manner, that the artificial introduction of a substance such as glucose directly into the circulatory system must necessarily alter many factors in the control of the volume and constituents of the blood, and that mass action of the substance

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14. Bollman, J. L.; Mann, F. C., and Magath, T. B.: Studies of the Physiology of the Liver. XII. Muscle Glycogen Following Removal of the Liver, Am. J. Physiol. **76**:238-248, 1925.

injected is important in regard to the curve obtained, the importance of such objections is minimized by the facts that the routine procedures were carefully standardized and the same with each animal and that the results were only considered on a comparative basis. As the total amount of glucose injected was relatively small, the amount excreted by the kidneys was negligible. As only trained animals were used, the effect of extraneous conditions on the blood sugar level could also be ignored.

The procedure we employed as a routine for performing a glucose tolerance test was as follows: The animal fasted for a period of from sixteen to eighteen hours previous to the test; blood samples were

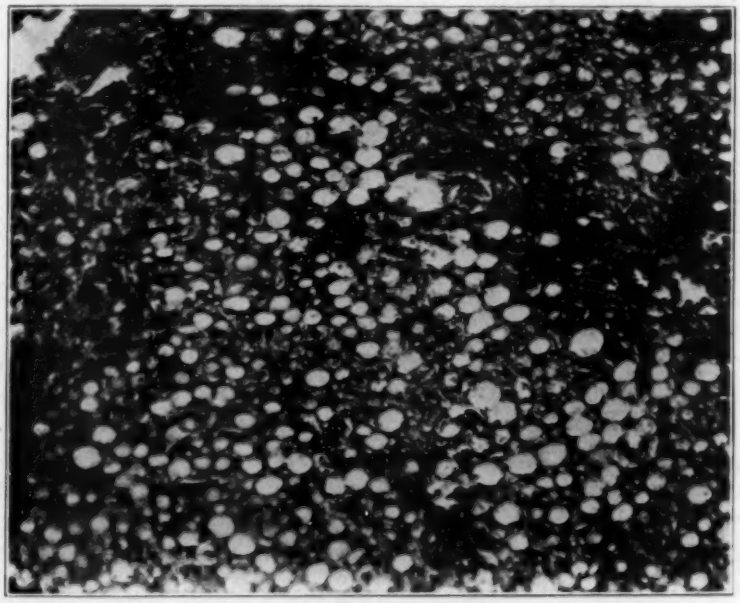

Fig. 4.—Section of liver removed seven months after partial removal of the liver and twelve months after Eck's fistula had been made. It was estimated that 30 per cent of the hepatic tissue remained after operation. The animal is alive and in fair condition four months after removal of the specimen; × 120.

obtained from the jugular vein, and the glucose was injected into the opposite jugular vein or a saphenous vein. The amount of glucose injected was either 0.25 or 0.5 Gm. for each kilogram of body weight and was injected in a 50 per cent solution. Two of the standard methods of determining the amount of blood sugar have been employed.[15]

15. Benedict, S. R.: A Modification of the Lewis-Benedict Method for the Determination of Sugar in the Blood, J. Biol. Chem. **34**:203-207, 1918. Folin, Otto; and Wu, Hsien: A System of Blood Analysis, J. Biol. Chem. **38**:81-110, 1919.

Blood specimens were secured at definite intervals after injection. We found that five, fifteen and thirty minutes and then every half hour for a total of two hours gave the most comparable curves. It is essential that the time of obtaining the blood sample in relation to the time of injection be accurate.

We have made standard glucose tolerance tests on a large number of normal dogs; on animals in which an Eck fistula has been made, on animals in which the amount of hepatic tissue has been greatly reduced permanently and on animals from which the liver had been totally removed. In several experiments the test was made on the same animal when normal, after an Eck fistula had been made, and after the amount of hepatic tissue had been reduced. Altogether several hundred tests of glucose tolerance have been made. When a standard glucose tolerance test, as described, is administered to a normal dog on successive days, blood sugar curves are obtained which are almost identical and can be superimposed. While the different normal animals varied somewhat, the variation was only within narrow limits. The important factor in the test was the time at which the blood sugar returned to the level that was obtained before injection. In normal animals this varied from thirty to sixty minutes after the injection of 0.5 Gm. of glucose for each kilogram of body weight. When the standard glucose tolerance test was given to an animal in which the portal blood had been diverted from the liver, there was usually a delay in the rate at which the blood sugar returned to the original level, although the time consumed was usually only the maximal for the normal animal, that is, one hour. If the amount of hepatic tissue of the animal with an Eck fistula was greatly reduced, the rate of disappearance of glucose from the blood stream was also reduced; but while the retardation was definite, it was usually very little greater than the maximal fluctuation for the normal animal. The rate of disappearance of glucose injected into the totally dehepatized animal is greater than normal.

The results of these experiments clearly indicate that the rate of disappearance of injected glucose from the blood stream, that is, the blood sugar curve following an intravenous glucose tolerance test, is modified somewhat by the condition of the liver. When the blood flow through the liver is decreased or when there is an actual reduction of hepatic tissue, the rate of disappearance of the injected glucose is slightly but measurably delayed. The more rapid rate of disappearance found after total removal of the liver is due to the loss of the regulatory action of the organ.

While the rate of disappearance of glucose from the blood stream is modified by the condition of the liver, a glucose tolerance test does not seem feasible as a measure of hepatic function because other factors besides the liver profoundly affect the rate at which glucose leaves the

blood stream. Only two of these need be mentioned: the effect of loss or damage of the pancreas and the effect of fasting. The liver and pancreas have a reciprocal action in regard to blood sugar. When the function of the pancreas is impaired or lost, the liver actively maintains a higher blood sugar level, so that any further addition of glucose to the blood stream enhances the effect of hepatic function and does not put it to a test. When a normal animal fasts for four or five days before the glucose tolerance test, the rate at which the glucose returns to preinjection level is greatly retarded, much more so than it has been possible to obtain in animals in which the amount of hepatic tissue had been permanently reduced. This delay in the rate of disappearance of

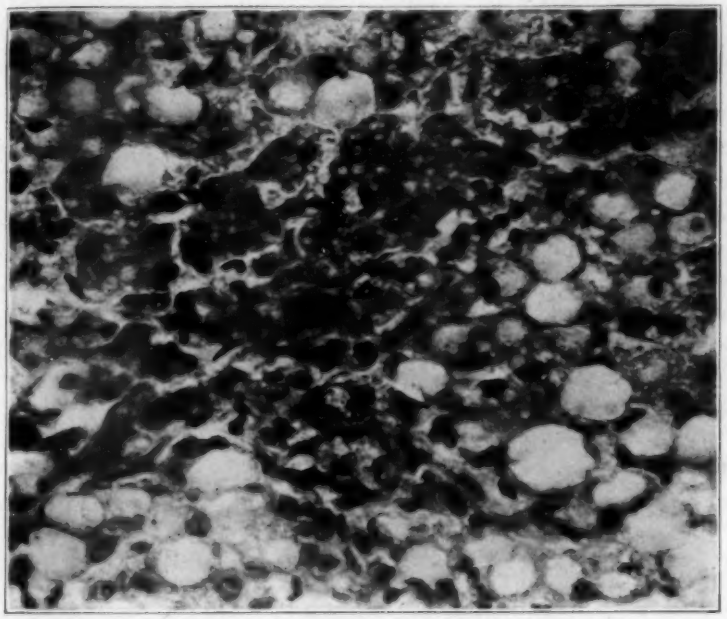

Fig. 5.—Higher magnification of section shown in figure 4. The field selected was the most normal of any that could be found; × 350.

glucose from the blood stream following injection in fasting animal is not dependent on the liver, because under suitable conditions it can be observed in the totally dehepatized animal; this delay also occurs in one with an Eck fistula and one with a reduced amount of hepatic tissue.

The levulose tolerance test as a test for hepatic function is based on the assumption that the liver is essential for the utilization of levulose. An historic review of the development of the test is given by Greene, Snell and Walters. This test has undergone the same modification in procedure as the glucose tolerance test, and the current method of administering the levulose is by mouth. If the increase in levulose

in the blood above a certain level following oral administration is due to decrease in hepatic function, it would appear that this effect should be exaggerated if the sugar were administered intravenously. We therefore carried out our levulose tolerance tests in the same way as the glucose tolerance test.

In general, the results of the experiments with levulose were the same as with glucose except that they were more variable. These results seemed to indicate that levulose did not furnish a good test of hepatic function. Furthermore, the same objections in regard to the changes in the blood sugar level produced by loss or damage to the pancreas as presented against glucose are also as fully justified in regard to levulose. However, definite evidence that levulose cannot furnish a specific test of hepatic function was obtained in some experiments on the totally dehepatized animal. The hypoglycemic condition which follows total removal of the liver is relieved by glucose only or by other substances, such as maltose and glycogen, which may be converted into glucose in the blood stream.[16] Levulose will not restore the hypoglycemic dehepatized animal to normal. However, if the intravenous administration of levulose to a dehepatized animal in suitable amounts is begun immediately after removal of the liver, the animal will be maintained in a fairly normal appearing condition for many hours and never manifest the hypoglycemic condition. These results prove that levulose will replace glucose to a considerable extent in the dehepatized animal if sufficient time is given for it to become effective. This would appear to be evidence that the levulose tolerance test cannot be a specific test for hepatic function.

TESTS OF HEPATIC FUNCTION BASED ON A CONSIDERATION OF THE RELATION OF THE LIVER TO PROTEIN METABOLISM

When the liver is totally removed from a dog, protein metabolism is greatly altered. The urea of the blood and tissues rapidly decreases as the urea is eliminated by the kidneys, and within a few hours the urea content of the urine also decreases, so that the blood, tissues and urine contain only minimal amounts of urea about twelve hours after total removal of the liver.[17] It has been shown that the amount of urea eliminated in the urine following complete removal of the liver is only that amount which is lost by the blood and tissues. We have been unable to demonstrate any formation of urea in the dehepatized dog

16. Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver. III. The Effect of Administration of Glucose in the Condition Following Total Extirpation of the Liver, Arch. Int. Med. **30**:171-181, 1922.

17. Bollman, J. L.; Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver. VIII. Effect of Total Removal of the Liver on the Formation of Urea, Am. J. Physiol. **69**:371-392, 1924.

even following injections of amino-acids or ammonia, as these substances remain unchanged in the blood and tissues of the liverless dog, except for the portion which is excreted unchanged in the urine. Coincident with the cessation of urea formation there is an accumulation of amino-acids in the blood, urine and tissues of the dehepatized dog. The increased amino-acid nitrogen of the blood and urine is distinct, but it is not of a magnitude comparable to the absence of urea nitrogen, because of the very great absorption of amino-acid nitrogen by the muscles. The injection of amino-acids into these animals increases the amino-acid content of the urine, but the greater part of the amino-acids is absorbed by the muscles and may be recovered there unchanged.

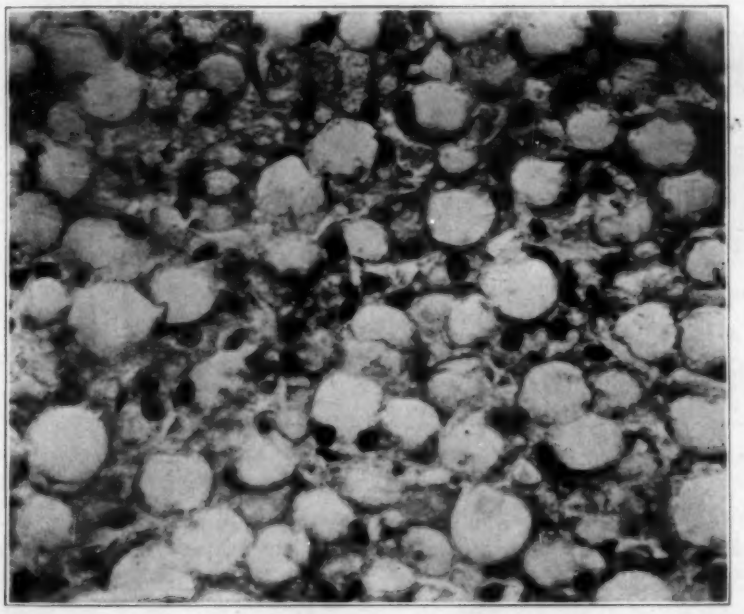

Fig. 6.—Same section of liver as shown in figures 4 and 5. This is a typical field and shows that the liver is far from normal; however, very little evidence could be obtained by means of the tests of liver function that this liver was both damaged and decreased in amount; × 350.

Although urea formation in the body depends entirely on the presence of the liver, since there is no formation of urea in the dehepatized animal, we have not been able to demonstrate any decrease in its formation even in those animals with the greatest reduction in the amount of hepatic tissue. The total amount of urea nitrogen in the urine of fasting animals is approximately the same whether they are normal or have been subjected to an Eck fistula, or been deprived of most of their hepatic tissue. The amount of urinary urea is increased by increases in the protein content of the diet. The ingestion of 300 cc. of milk by

dogs with the greatest reduction in the amount of hepatic tissue, produces an excretion of urea in the following twenty-four hours which is almost identical with that of a normal animal on the same diet. The ingestion of 300 Gm. of meat also failed to bring out any difference in the excretion of urea which could be attributed to differences in the amount of hepatic tissue in the animals observed. There was evident, however, the diminution of the percentage of the total nitrogen excreted as urea by those animals having an Eck fistula, but subsequent removal of the major portion of the liver failed to produce any further reduction of the urea percentage. This reduction is produced largely by an increase in the excretion of ammonia, which is probably not directly attributable to hepatic damage, since similar changes may be produced by any condition which alters the acid-base equilibrium of the body toward the acid reaction.

The cessation of urea formation in the totally dehepatized dog allows the accumulation of increased amounts of amino-acids in the blood, urine and tissues. Since the greater part of this amino-acid nitrogen is absorbed by the muscles and only the minor part is found in the blood and urine, it is not surprising that studies of the amino-acid content of the blood and urine have not shown great changes due to partial removal of the liver. This fact may also have considerable bearing on the amount of amino-acid in the blood and urine in disease. We have found no significant quantitative changes in the amino-acid nitrogen of the blood even in the animals with the greatest reduction in the amount of hepatic tissue, and the amount of amino-acid nitrogen excreted in the urine of these animals has been but slightly greater than that of normal animals. The use of diets of moderate or excessive content of protein has also failed to bring out any great differences. The same may be said for the intravenous injection of glycocol or alanin, since these amino-acids remain in the blood and appear in the urine in only slightly greater amounts after a large amount of hepatic tissue has been removed. It is noticeable, however, that the tolerance for intravenous injections of alanin or glycocol is greatly diminished by a reduction in the amount of hepatic tissue. The injection of amounts of amino-acids that are without visible effect in a normal animal produces cardiac irregularity, increased respiration and often collapse of animals if the amount of hepatic tissue has been greatly reduced. The dehepatized dog will not survive the rapid injection of large amounts of amino-acids which do not produce symptoms in the normal animal.

Leucin and tyrosin have not been found in the urine of dehepatized animals, nor have we detected any leucinuria or tyrosinuria in animals in which the quantity of hepatic tissue had been greatly reduced. It would seem that these substances are products of necrosis of the liver and that their presence is not due to the absence of hepatic tissue.

Changes in the ammonia content of the blood and urine do not seem to be directly referable to the amount of hepatic tissue present. Following complete ablation of the liver there is a slight rise in the ammonia content of the blood and a marked rise in the ammonia content of the urine. The relative amount of ammonia nitrogen of the urine increases because of the decrease of the urea nitrogen, but the absolute amount of ammonia of the urine decreases rapidly after the first few hours. The amounts of ammonia which appear in the urine after the eighteenth hour are small enough to be considered as of intestinal origin. The intravenous injection of ammonia is not tolerated well by the dehepatized animal, since the ammonia remains unchanged in the blood and tissues and is not converted into urea as it is normally. The amount of ammonia in the urine of dogs with an Eck fistula is greater than that of normal animals on the same diet, but further reduction in the amount of hepatic tissue in an animal with an Eck fistula produces no noticeable change in the quantity of ammonia excreted.

The complete removal of the liver of dogs produces a great increase in the uric acid content of the blood and tissues and causes the appearance of large amounts of uric acid in the urine.[18] This has been shown to be due to the complete failure of the liverless dog to destroy uric acid. Uric acid injected into the dehepatized dog remains unchanged in the blood and tissues and is excreted unchanged in the urine. The destruction of uric acid in the normal dog seems to be entirely dependent on the presence of the liver since no uric acid is destroyed in the absence of the liver and no other means of influencing the destruction of uric acid has been demonstrated.

Following the intravenous injection of 40 mg. of uric acid[19] for each kilogram of body weight of the normal dog, there is a rapid disappearance of the excess uric acid in the blood and only a very small increase in the uric acid in the urine.[20] When this amount of uric acid is injected into a dog having an Eck fistula, the disappearance of the uric acid is somewhat delayed and a slight increase in uric acid excretion occurs. Further reduction of the amount of hepatic tissue gives rise to greater delay in the disappearance of the injected uric acid from the blood, and the urinary excretion of uric acid is increased. Both the

18. Bollman, J. L.; Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver. X. Uric Acid Following Total Removal of the Liver, Am. J. Physiol, **72**:629-646, 1925.

19. Uric acid solutions for intravenous injection were prepared by adding sufficient uric acid to a warm saturated solution of lithium carbonate so that a 2 per cent solution of uric acid was obtained.

20. Folin, Otto: Berglund, H., and Derick, C.: The Uric Acid Problem, an Experimental Study on Animals and Man Including Gouty Subjects, J. Biol. Chem. **60**:361-471, 1924.

reduction of the rate of disappearance and the amount of uric acid appearing in the urine are greater the greater the reduction in the amount of hepatic tissue. Two objections should be raised to the use of uric acid injections as a test of hepatic function; first, large injections of uric acid produce severe lesions in the kidneys and interfere with excretion; second, lesions of the kidneys may cause retention of uric acid as uric-acidemia in man, although in the dog the presence or absence of the kidneys is without effect on the rate of disappearance of this amount of uric acid from the blood.

Studies on the uric acid in the blood and urine have been most satisfactory in showing increase in uric acid which was roughly proportional to the extent of the reduction of hepatic tissue. Normal dogs have but a trace of uric acid in the blood and excrete but a trace in the urine. Following the institution of an Eck fistula, these animals under fasting conditions have a tendency toward a higher level of uric acid in the blood, and the amount of uric acid in the urine is greatly increased. After further reduction of hepatic tissue, the uric acid of the blood is found to be increased, and may contain as much as ten times the normal amount of uric acid for a few weeks after removal of the major portion of the liver. Any further increase in the uric acid of the blood has invariably been attended by the failure and subsequent death of the animal, and at necrospy it has been found that the liver has been reduced at operation or has atrophied to a minimal amount. The amount of uric acid in the urine of the fasting animal is also increased by reduction in the amount of the hepatic tissue. Under ordinary dietary conditions the amount of uric acid in the urine is increased over the fasting level, and a greater increase appears in those animals with the greater reduction in the amount of hepatic tissue.

With a diet [21] of high purin content, the uric acid excretion of normal dogs may be increased to a measurable amount and is quite constant for a given diet. After the production of an Eck fistula, dogs on the same diet excrete from two to four times the normal amount of uric acid, and it has been observed at operation and at necropsy that the liver is more atrophic in those dogs excreting the greater amounts of uric acid. The removal of portions of the liver from these animals gives rise to a greater excretion of uric acid in the urine when these animals are subjected to this same diet. In this way we have obtained as much as 800 mg. of uric acid in the daily urine of a dog whose liver has been greatly reduced in size. It would appear that the amount of uric acid in the urine of persons on high purin diets might serve as some index of hepatic efficiency.

21. One hundred and seventy-five grams of fresh pancreas of the horse.

HEPATIC EXCRETION OF DYES AS A CLINICAL INDICATION OF DERANGED HEPATIC FUNCTION

The use of the excretion of phenoltetrachlorphthalein by the liver as a test for hepatic efficiency in disease was introduced by Rowntree, Hurwitz and Bloomfield [22] in 1913. Since that time this test has been considerably modified and standardized, so that now the behavior of phenoltetrachlorphthalein has undoubtedly been studied more than any test of hepatic function. The large amount of clinical and pathologic data which has thus accumulated is of great value in the interpretation of the results of this test.

In our studies of phenoltetrachlorphthalein we have employed the technic of Rosenthal [23] in observing the rate of disappearance of the dye from the blood stream following intravenous injection of 5 mg. of the dye for each kilogram of body weight of the animal. Blood was withdrawn and the amount of dye remaining in the plasma was determined at intervals of 5, 15, 30, 60, 90 and 120 minutes after injection. Further specimens of blood were withdrawn at appropriate intervals after this time, providing the dye was still present in the plasma. The results with this dye were striking in showing the difference between a normal and a dehepatized dog. In the normal dog only a small amount of the dye was found in the circulating blood five minutes after injection, and within thirty minutes after injection the dye had completely disappeared from the blood. With the dehepatized dog about five times as much dye was present in the blood five minutes after injection, and no appreciable decrease in the dye content of the blood could be determined for about ten hours. Even fifteen hours after injection three times as much dye was present in the blood of the dehepatized dog as was found in the blood of normal dogs five minutes after injection.

The results with phenoltetrachlorphthalein injections in animals in which the amount of hepatic tissue had been definitely reduced were not so gratifying. We could detect no difference in the rate of disappearance of the dye from the blood of dogs whether they were normal or had been reduced to the least possible amount of hepatic tissue with which we could maintain life. Because the rate of disappearance of the dye from normal animals was so rapid, we decided to double the amount of dye injected, so that a definite curve of the rate of its disappearance could be obtained. The blood of the normal dogs became free from dye about two hours after the intravenous injection of 10 mg. of

22. Rowntree, L. G.; Hurwitz, S. H., and Bloomfield, A. L.: An Experimental and Clinical Study of the Value of Phenoltetrachlorphthalein as a Test for Hepatic Function, Bull. Johns Hopkins Hosp. **24**:327-342, 1913.

23. Rosenthal, S. M.: An Improved Method for Using Phenoltetrachlorphthalein as a Liver Function Test, J. Pharmacol. & Exper. Therap. **19**:385-391, 1922.

phenoltetrachlorphthalein for each kilogram of body weight. Even with this dosage the dye disappeared from the blood of animals with an Eck fistula at exactly the same rate as in normal animals. Only in those animals with the greatest possible reduction of hepatic tissue were we able to demonstrate any retention of the dye, and even in these the retention was so slight that it would not ordinarily be considered.

It was thought that a further increase of the amount of dye injected would serve to bring out larger differences in the rate of its disappearance. However, we have been unable to demonstrate this to any satisfactory degree, because the animals were unable to withstand a dosage which is without noticeable effect in the normal animal. This same increase in toxicity due to reduction in the amount of hepatic tissue has also been observed with the phenoltetrabromphthalein and phenoltetraiodophthalein used in cholecystographic studies.

More recently the use of bromsulphalein [24] in place of phenoltetrachlorphthalein has been advocated. This dye is somewhat more satisfactory to use because of the ease with which it dissolves in water and also because it is not irritating. Bromsulphalein does not disappear from the blood of normal dogs as rapidly as phenoltetrachlorphthalein, but with the dosage of 5 mg. for each kilogram of body weight no difference from normal is obtained in the rate of disappearance of the dye from the blood of dogs with an Eck fistula. If the amount of hepatic tissue is greatly reduced, there is a definite though small retention of this dye. By the injection of double this amount of bromsulphalein a rather indefinite retention of the dye may be observed in some animals with an Eck fistula. Further reduction of the amount of hepatic tissue in such animals produces a definite retention of the dye, which is most marked in those that have lost the greatest amount of hepatic tissue. In no case, however, have we been able to obtain the degree of retention which might be expected from the amount of damage to the liver, nor is the retention to be compared with that obtained in cases of obstructive jaundice, or in cases of complete absence of the liver.

Our experience with rose bengal has not been so extensive, but in general our findings with its use are almost similar to those with bromsulphalein. With the same total amount of rose bengal in the case of the dog as is recommended by Kerr [25] and his associates for use in man, we have been able to demonstrate definite retention of the dye in animals with an Eck fistula and a greater retention in animals with a greatly reduced amount of hepatic tissue. When rose bengal is given in

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24. Rosenthal, S. M., and White, E. C.: Clinical Application of the Bromsulphalein Test for Hepatic Function, J. A. M. A. **84**:1112-1114, 1925.

25. Kerr, W. J.; Delprat, G. D.; Epstein, N. N., and Dunievitz, Max: The Rose Bengal Test for Liver Function. Studies on the Rate of Elimination from the Circulation in Man, J. A. M. A. **85**:942-946, 1925.

amounts comparable to those recommended for man, this difference in the rate of disappearance is greatly reduced and would ordinarily be overlooked.

Tests of Hepatic Function Based on the Detoxifying Ability of the Liver.—The anatomic relations of the liver make its situation particularly advantageous for determining the disposition of substances entering the blood from the gastro-intestinal tract. This advantage is threefold: All of the blood containing substances absorbed from the digestive tract must pass through the liver; by means of the extensive capillary bed of the liver all of this blood is exposed to the greatest number of hepatic cells, and the biliary system provides a means of immediate excretion, so that some substances might be entirely prevented from entering the general circulation. Therefore it is not surprising that the liver should be regarded as the guardian of the body against the general dissemination of toxic substances from the intestines. Its protective function is more evident in the light of the relation of the liver to the metabolism of carbohydrates and the relation of the latter to detoxication. It has been shown that this organ is responsible for the maintenance of the sugar in the blood and that it maintains a stored supply of glycogen. The importance of glucose to oxidations within the body is well illustrated by the accumulation of incompletely oxidized fatty acids when glucose metabolism is deranged, and it seems probable that the oxidation of other toxic substances in the body depends on the availability of sufficient amounts of glucose.[26] The resistance of animals to phosphorus and chloroform poisoning [27] when their livers are well filled with glycogen has been considered as evidence of the accuracy of this statement. Again, the relation of the liver to the deaminization of amino-acids and to urea formation may be offered as proof of detoxicating activity. In our experiments with complete removal of the liver, we have shown that the deaminization of amino-acids does not occur in the absence of the liver and also that the tolerance of liverless animals to injections of amino-acids is greatly reduced. We have also shown that ammonia is not converted into urea in the absence of the liver and that injections of ammonium salts are markedly more toxic to animals deprived of their livers. We have also observed a decreased tolerance for phenol, benzoic acid, phenoltetrachlorphthalein and several other toxic substances in the liverless dog. This same increased susceptibility to toxic agents has been observed, to a lesser degree, in animals with a greatly reduced amount of hepatic tissue.

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26. Bollman, J. L.: Experimental Observations on Glucose as a Therapeutic Agent, Surg. Clin. N. Amer. **5**:871-880, 1925.

27. Graham, E. A.: The Resistance of Pups to Late Chloroform Poisoning in Its Relation to Liver Glycogen, J. Exper. Med. **21**:185-191, 1915

Although the physiologic reaction of liverless animals demonstrated that they were more subject to the toxic action of phenol [28] and benzoic acid,[29] we have been unable to demonstrate any reduction in rate of the conjugation of either of these substances. The rate of conjugation of phenol injected into the blood of the liverless animal is little altered from that of normal animals; the free phenol in the blood rapidly returns to normal, and there is an increase in the amount of conjugated phenol in the blood. For this reason it would seem that the conjugation of etheral sulphates may take place outside of the liver and that tests of hepatic function based on this conjugation must be of questionable value. In the same way we have shown that synthesis of hippuric acid occurs in the dehepatized animal following the injection of sodium benzoate.

Excretion of glycuronic acid [30] following the ingestion of camphor occurs in animals deprived of the major portion of the liver, and we have failed to observe any diminution in the amount of glycuronates excreted following the ingestion of camphor even in the animals with greatest reduction in the amount of hepatic tissue However, we have used only qualitative tests for glycuronic acid, and it is entirely possible that the elaboration of methods for their quantitative determination might show these results to be in error. The concentration of salicylic acid in the urine [31] may be estimated roughly by the amount of color appearing after the addition of a few drops of dilute solution of ferric chloride. Intravenous injection of 5 mg. of sodium salicylate for each kilogram of body weight is followed in the next three hours by the excretion of only a trace of unconjugated salicylic acid by the normal dog. Following the production of an Eck fistula, animals receiving an identical amount of salicylate excrete a noticeably larger amount in the urine. Further reduction of the amount of hepatic tissue in these animals, however, has failed to cause any greater excretion of the uncombined salicylates in the urine following the administration of the same dosage.

Following the ingestion of a meal containing protein there is a slight rise of arterial pressure and a definite leukocytosis of two or three hours' duration. Widal [32] has described a group of cases in

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28. Pelkan, K. F., and Whipple, G. H.: Studies of Liver Function. III. Phenol Conjugation as Influenced by Liver Injury and Insufficiency, J. Biol. Chem. **1**:513-526, 1922.

29. Delprat, G. D., and Whipple, G. H.: Studies of Liver Function, Benzoate Administration and Hippuric Acid Synthesis, J. Biol. Chem. **49**:229-246, 1921.

30. Roger, H., and Chiray, M.: La glucuronurie normale et pathologique; ses variations dans la cirrhose et le diabete, Bull. Acad. de med. **73**:446-449, 1915.

31. Roch, M.: Salicylate Test of Liver Function, Rev. med. de la Suisse, **42**: 291-295, 1922.

32. Widal, F.; Abrami, P., and Iancovesco, N.: L'epreuve de l'hemoclasie digestive dans l'etude de l'insuffisance hepatique, Presse méd. **2**:893-898, 1920

which the reverse has been true, that is, there was a decline of blood pressure and an absence of leukocytosis or even leukopenia. This he attributes to the failure of the liver to remove certain peptones which have passed into the portal circulation from the intestines and have entered the general circulation, producing the drop in blood pressure and leukopenia. This hemoclastic crisis is determined by observations of the changes in the leukocyte count of the fasting animal at thirty-minute intervals following a meal of 200 cc. of milk. Our experience with this test has not been satisfactory in the dog. Many presumably normal dogs showed the typical leukopenia of hemoclastic shock at times, and at other times manifested a normal leukocytosis under the same conditions. In the same way we have found at different times the typical leukopenia of hemoclysis or the typical normal leukocytosis in animals with a greatly reduced amount of hepatic tissue.

The Clot-Forming Elements of the Blood in Hepatic Deficiency.—We have been unable to demonstrate any consistent changes in the clot-forming elements of the blood in dogs following complete removal of the liver. The calcium content of the blood remains within normal limits and the amount of fibrin obtained from the clotted blood is not abnormal, nor have we determined any markedly delayed coagulation time of the blood of dogs after the complete removal of the liver. However, the coagulation time and the fibrin content of the blood under these conditions vary widely, but since the same variations occur in normal animals, too great significance cannot be attached to these results. Again, the coagulation time and fibrin content of the blood of animals with greatly reduced amount of hepatic tissue are subject to considerable variation. In general, there is a slight delay in the coagulation time in these animals, and the fibrin content of the blood rather tends toward the lower limits of normal. However, the presence of slight infection of the wound gives rise to an increase in the coagulation time, and the fibrin content of the blood rises toward the upper limits of normal. It would appear that the liver did exert considerable influence on the clot-forming elements [33] of the blood, but that a number of other factors must also be considered.

COMMENT

As the liver has so many important functions, it would seem easy to elaborate a method of measuring the capacity of the liver when normal and when diseased in at least one of these functions. This has not been possible up to the present time. For this failure there have been

33. Foster, D. P., and Whipple, G. H.: Blood Fibrin Studies. IV. Fibrin Values Influenced by Cell Injury, Inflammation, Intoxication, Liver Injury and the Eck Fistula, Am. J. Physiol. **58**:407-431, 1921.

two main causes: (1) While the liver is of major importance in many phases of physiologic activity, its activity is only a part of these processes, other organs or tissues being necessarily involved; (2) in many of these processes the liver stubbornly maintains its activity, and hepatic insufficiency and death are concomitant. The intimate relation of the function of the liver to many general physiologic phenomena and the function of other organs has been discussed in relation to carbohydrate metabolism and the formation of bilirubin. Other examples could be given to illustrate how extremely difficult it is to separate the specific activity of the liver from the general activity of the organism. As so many functions of the liver are of the greatest importance, it would be anticipated that they would be maintained even under most adverse circumstances. Such has been found to be the case, as in the maintenance of the blood sugar level and formation of urea.

Our experiments on animals with permanent reduction in the amount of hepatic tissue are open to a few just criticisms. In order to prevent regeneration of the liver it was necessary to eliminate the most important source of blood supply to the organ. This would appear to differ considerably from the condition of spontaneous disease. However, the portal blood supply is markedly diminished in some diseases of the liver as demonstrated recently by McIndoe and Counsellor.[34] After all, it may be that the diminution of hepatic tissue affects only the reserve of the organ, and does not put it under a stress comparable to that produced by disease. However, some of our animals did die apparently from insufficiency of an unknown hepatic function; a carefully controlled diet was necessary to maintain the animal in a normal appearing condition, and at least one diet, that of pancreas, did show evidence of producing a functional strain, as did also the intravenous injection of such substances as amino-acid, phenol and dyes. Finally, it must be pointed out that simple reduction of the amount of tissue of an organ does not produce the same effect as disease of the organ. Histologic examination of a specimen of liver from which the portal blood has been diverted and the size of which has been reduced surgically shows definite and marked changes not unlike the picture seen in many diseases. While the method has some pertinent objections, it is the best means we have been able to find to reduce the amount of hepatic tissue permanently, and with it we are confident we have been able to reduce the functional potentiality of the liver in many instances to considerably less than one-fifth the normal. After all, a test of hepatic function which will not afford at least a hint of hepatic disease

34. McIndoe, A. H., and Counsellor, V. S.: Studies in the Vascular and Biliary Trees of the Liver, presented at the American Society for Experimental Pathology, Cleveland, Ohio, December, 1925.

when hepatic function is less than one-fifth normal will probably not be of much clinical value as a test of hepatic function.

Many pertinent questions arise in regard to the varied functions of the liver in relation to tests of hepatic function. Only a few of these questions can be presented. Do all liver cells have the same capacity for all the functions of the liver, or is there a division of function between the various cells of a lobule? It is possible that the liver cells near the periphery of the lobule where they receive the incoming blood first perform a different group of functions than do those around the central vein. They may all perform the same function, but some are intermittently inactive in the same manner as the capillaries have been shown to be. There is some evidence that the activity of the different lobes of the liver varies, on account of the fact that mixing of the portal blood is not complete, and some lobes of the liver receive more blood from one part of the portal system than do other lobes. Again, are all functions of the liver impaired equally in a given disease, or are some of the functions impaired more easily, or in a different manner from others? These questions are pertinent to the legitimacy of tests of hepatic function, and a complete solution of the problem may not be forthcoming until they are answered. We have undoubted proof that there is a dissociation of functions of the liver and that some of the functions are impaired more easily than others. Only one example will be given. The animal with an Eck fistula can excrete the bile pigment without showing any evidence of jaundice or sufficient amount of pigment in the blood to give a van den Bergh test. In parallel with this there is also no retention of dye. On the other hand, there is a definite and measurable decrease in the ability of such an animal to destroy uric acid. It is obvious that if one function of the liver is more easily impaired than the other functions by a majority of the lesions affecting the organ, a test for such a function would be the most valuable.

The known functions of the liver, named in the order in which they appear to be the most easily impaired as studied in the dog, are: (1) the ability to destroy uric acid, (2) the excretion of bile pigment, and (3) the ability to prevent reaction from the administration of certain toxic substances. There is no question that of all the physiologic reactions in relation to the liver and all the tests suggested for estimating hepatic function which we have studied, the function of the liver in relation to the destruction of uric acid is the most easily impaired. We can obtain evidence of impairment of hepatic function by determining the rate of destruction of uric acid in an animal in which no other evidence of decreased hepatic function can be obtained. Even a slight period of asphyxia will often produce a measurable accumulation of uric acid in the blood of some animals, which, while it may be the result of an increase of neucleoproteins following increased destruction of cells by

the state of asphyxia, is more easily explained on the basis of hepatic damage. While it has been repeatedly shown that the liver has a great reserve capacity to excrete bile pigment, it is a function of the liver which is readily impaired. A normal dog, from which 70 per cent of its liver has been removed at one time, develops transitory bilirubinemia, while an animal with an Eck fistula which has lost an equal amount of hepatic tissue will exhibit more intense and prolonged bilirubinemia. Finally, the increased susceptibility of animals with reduced liver to react with symptoms of toxicity to the administration of many substances such as lactic acid and ammonia, in amounts which on the basis of body weight will cause no reaction in the normal animal, bespeaks some hepatic function relatively easily impaired.

While we have found it almost impossible to devise any test which will even give a hint of impaired hepatic function, even when the total amount of hepatic tissue has been greatly reduced, we have made some general observations which would indicate that actual hepatic insufficiency was present. For instance, it is a well-known fact that an animal with an Eck fistula, while seeming normal in many respects, needs careful attention in some respects, particularly diet. However, the meat intoxication of such an animal that occasionally occurs may not be the result of disturbed hepatic function, but rather of a change in the function of the gastro-intestinal tract due to altered venous drainage and pressure. Some animals with an Eck fistula do not thrive, regardless of care and diet, and eventually die from some cause so far unknown. A carefully controlled diet, such as one of milk and syrup, is necessary to keep the animals in a normal appearing condition. Operation on an animal with an Eck fistula may be attended by much greater risk than normal even if to all general appearances the animal seems normal and responds normally to all tests except that of ability to destroy uric acid. The mortality rate of partial hepatectomy in animals with an Eck fistula has been much higher than in normal animals, although the general condition of the two groups of animals might appear the same. Many of our animals with greatly reduced amounts of hepatic tissue have gradually failed and died without exhibiting any particular evidence of known hepatic insufficiency.

These observations would appear to show that the liver must have some subtle and at present unknown function or functions which apparently are impaired more readily than most of its known functions. It is possible that failure or impairment of such an unknown function may be responsible for some of the deaths that follow surgical procedures and for which no adequate cause can be found at necropsy. It should be noted that, if this is true, none of the tests of hepatic function yet devised will indicate such insufficiency of the organ. In this connection it should be noted that the production of a reaction by several

of the substances injected, in the dog with a reduced amount of hepatic tissue and not in the normal animal, was more indicative of hepatic damage in the degree of toxic symptoms produced than in the routine method of estimation. That the employment of such substances in animals with decreased hepatic function is not without damage, is proved by the fact that several of our animals with a reduced amount of hepatic tissue succumbed a few days after making such a test.

SUMMARY

The most important of the tests suggested for measuring hepatic function have been studied in normal animals, animals with an Eck fistula, animals with permanently reduced amounts of hepatic tissue and animals with the liver completely removed. As a result of these observations, a few positive statements can be made relative to the functional capacity of the liver, a few suggestive signs of hepatic deficiency can be presented, and the tests of hepatic function suggested can be evaluated by means of a standard technic.

The bilirubinemia which follows removal of the greater portion of the liver is but transitory, and the remaining portion of the liver is soon able to excrete all of the bile pigment formed in the animal. Partial removal of the liver has little demonstrable effect on the rate of disappearance of dyes injected into the blood unless the amount of dye injected is excessive, although complete retention of the dye is easily demonstrated in the completely dehepatized animal. The carbohydrate metabolism of animals with greatly reduced amounts of hepatic tissue, so far as tests of hepatic function are an indication, is also maintained at an approximately normal level, and only slight differences from normal may be found in the amount of sugar in the blood. The use of glucose or levulose tolerance tests also fails to bring out any marked deviation of these animals from normal. The marked changes in the formation of urea, accumulation of amino-acid and excretion of ammonia, which are specific in the dehepatized animal, are difficult to demonstrate in the animal with greatly reduced hepatic tissue. The decrease in the destruction of uric acid, however, may be demonstrated in animals with reduced hepatic tissue. Physiologic reactions following the administration of certain toxic substances may indicate that the reduction in the amount of hepatic tissue reduces the animal's tolerance to these substances, but the chemical tests employed do not show any extensive decrease in the rate of conjugation of these substances.

In summarizing the results of the experiments, as they would appear to apply to the clinical tests of hepatic function, the following can be suggested: There appears to be no physiologic basis for many of the tests employed to measure the functional capacity of the liver.

So far as carefully controlled experimental data may apply to such problems, most of the tests should be discarded. Some of these tests which could not be proved experimentally to have any value in a known and controlled condition of hepatic deficiency, may be of value clinically, either because they are an index of disease, not necessarily wholly hepatic, or because spontaneous disease of the liver may affect the function differently from experimental procedures, or because man may be somewhat different from the dog. However, the value of such tests should be accepted only with data obtained in cases in which the hepatic disease is proved either by a definite clinical diagnosis or anatomically at operation or necropsy.

The tests which would appear from these experimental data to have value in relation to estimation of the function of the liver are as follows: The van den Bergh tests for bilirubin in the blood should be of value as a measure of a condition in which the liver is either directly or indirectly, but not necessarily predominently, affected. The physiologic basis for the use of the dyes which have been employed as tests of hepatic function is the fact that they appear to be excreted mainly by the liver. Experimentally the hepatic function could not be sufficiently diminished to show a definite relation of hepatic insufficiency to retention of dye. Since, however, there is a definite retention of the dye in certain cases in man, this would appear to be one of those tests whose value can be determined only by its careful and controlled use clinically, as has been done by Rowntree and his associates. There is a definite experimental basis for the elaboration of a test of glycogen mobilization which might bear the same relation to the activity of the liver in relation to carbohydrate metabolism as the quantitative bilirubin test does to pigment metabolism.

The best test of functional deficiency of the liver in the dog which has been found is based on the facts that destruction of uric acid depends on the liver, that this is the most easily injured of the known functions of the liver, and that the amount of uric acid excreted in the urine appears to bear a definite relation to hepatic damage. This test is easily performed by determining the amount of uric acid eliminated in the urine during a standard period of time following the ingestion of a standard meal with high content of purin. Whether or not such a test will be of value in man remains to be proved.

BILHARZIA INFECTION IN AN APPARENTLY NORMAL APPENDIX

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Infection with *Schistosoma haematobium* (formerly called *Bilharzia bancrofti*) is considered rare in the northern states. The increasing afflux of colored people from the South will bring more cases of bilharziosis to the North. This may justify us in publishing the following case and in discussing a few points related to bilharziosis.

REPORT OF A CASE

History.—F. T., a colored woman, aged 26, came to the hospital complaining of diffuse vaginal discharge and backache. The clinical findings were retroversion of the uterus and endocervicitis. An operation for retroversion was performed, and the lacerated cervix was amputated. The appendix gave the impression of being subacutely inflamed, and an appendectomy was performed. Nothing in the previous history of the patient or in the clinical findings pointed toward an intestinal lesion.

Laboratory Findings.—The gross appearance of the appendix was normal. It was 7 cm. long and of normal thickness. Its serosa was slightly injected. The question is whether a thorough inspection, perhaps aided by a hand lens, would not have shown minute nodules. The appendix was fixed in a 4 per cent solution of formalin, and one slice from near the tip was embedded in paraffin. A section was stained with Delafield's hematoxylin and eosin. Under a low magnification the slide gave a picture as shown in figure 1. A provisional diagnosis of bilharziosis was made at once from the general appearance of the eggs and especially from their distribution in the tissue. After a short search typical spines were detected.

The tissue lesions in bilharziosis are caused by the egg. Neither the adult worm nor the larva gives rise to symptoms, so far as we know. Consequently, we have not much to say about the embryos situated in the shells. Some of them showed details of the miracidiol stage (fig. 6). In our opinion it will not do to regard the eggs just as foreign bodies in their relation to the tissue. Foreign body giant cells were present in the surroundings of only one egg among the large number found in the slides. The characteristic tissue formations surrounding most of the eggs indicate their definite influence on the tissue; and the complete absence of any reaction in other instances seems to show that the mere presence of the hard egg shell does not necessarily act as an irritant.

The characteristic tissue reaction in the appendix of this patient is shown in figures 7, 8 and 9. A loose ovoid or nearly ball-shaped tissue formation surrounded the remnants of the shell or of the whole ovum. In some of the formations only minute glassy spots in the center represented the last traces of the destroyed shell. We were not successful in demonstrating them in the photomicrographs. Early stages, however, showed the outline of the shell (fig. 7). In the inner layers the cells were swollen, their protoplasm seemed slight in density

and the nuclei were large and pale. The layers were not well separated from each other. In the periphery the layers were thinner and more distinct. The cells here were smaller and spindle-shaped, with dark and compact nuclei. Most of these cells were probably derived from connective tissue. In a more advanced stage (fig. 8) the center of the formation had become compact. It appeared to be composed of many thin layers between which some leukocytes were found. The aspect of the peripheral layers was similar to that in earlier stages, but they contained more nuclei of irregular variegated shape, similar to nuclei of leukocytes. Finally (fig. 9) the whole formation became more compact and more separated from the surrounding tissue. Probably these were not really final stages, but no fibrous hyaline or calcified nodules were found in the appendix.

The shell stained distinctly with Weigert's method for elastic fibers. The situation of the eggs bore no relation to the direction of the muscle fibers. In

Fig. 1.—Mucosa and submucosa of appendix. The more or less distinct remnants of several eggs can be seen; low magnification.

some instances doubt arose whether remnants of an egg shell were seen or remnants of a blood vessel. Since the eggs of *Schistosoma* frequently are caught in small blood vessels, both eggs and vessels may appear in these doubtful pictures.

The shell substance, which is very resistant to chemicals, was dissolved or at least completely destroyed by tissue action. Though we do not know anything definite about the way this is accomplished, the microscopic pictures seem to suggest that it is done in different ways: In some slides the shell appeared very thick with indefinite outlines as if it had been softened, while in others even the last minute remnants of shell were thin and had a sharp contour. Furthermore, the ends of broken pieces of the shell were straight in some eggs and coiled in others, thus indicating differences in elasticity.

To ascertain the extent to which other organs of the patient were infected with *Bilharzia* a piece of cervix and the feces and urine were available. In the

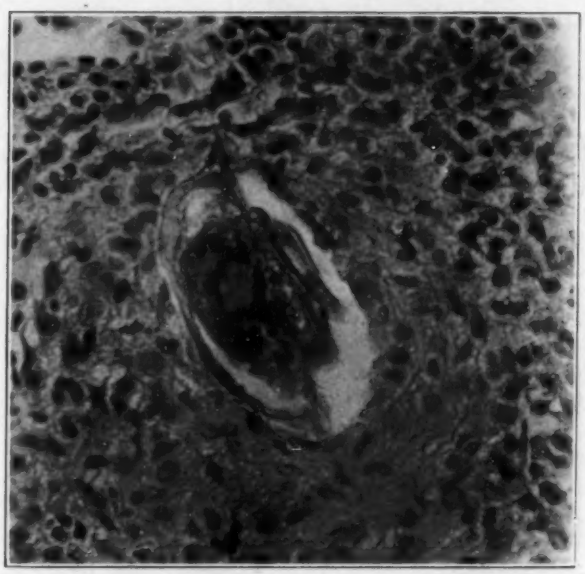

Fig. 2.—The shell of the egg is partly broken. The spine is polar; it is well preserved. The relative sizes of the high light area and the deep shadow area on the spine vary with the focusing. The surrounding tissue is concentrically arranged; high magnification.

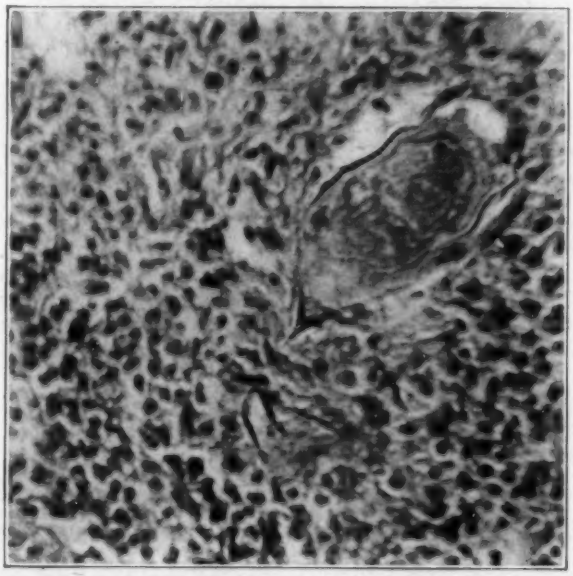

Fig. 3.—More destruction of the shell. The spine is well preserved. Near the spine the small remnants of another egg shell are seen.

cervix were found one calcified egg and one of the onion shell formations mentioned above. The cervical tissue was dissolved in antiformin, but no eggs could be found in the sediment. Several urinalyses failed to reveal ova. In the feces a few could be found, all of which had a lateral (ventral) spine. A male trichocephalus was found also but no eggs of trichocephalus. The number of eosinophils in the blood was normal. The Wassermann reaction was positive.

As can be seen from figure 10, the egg in the uterine cervix did not give origin to any tissue reaction. But the presence of the onion shell formation indicates that other ova in the cervix were destroyed by means of, or at least together with, an inflammatory process.

Subsequent Course.—The patient made an uneventful recovery. She is in good health now, two years after operation. This is not astonishing, since bilharziosis frequently heals without treatment if reinfection does not occur. Perhaps the

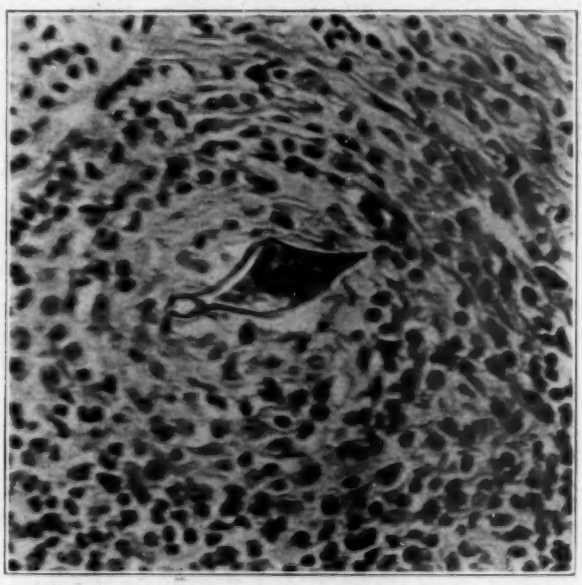

Fig. 4.—Shrunken egg with preserved polar spine; circular arrangement of surrounding tissue.

laparatomy had some effect also. Even patients with severe intestinal bilharziosis have made unexpected recoveries after an exploratory laparotomy. Surgeons have been the more impressed by such recoveries when a diagnosis of inoperable carcinoma of the intestine had been made at operation. The feces of the patient, two years after operation, still contain eggs of *Schistosoma.* In the urine none could be found.

COMMENT

A difficulty of demonstrating spines in tissue sections has been emphasized in the literature. No such difficulty existed in our case, and it is hoped that a comparison between figures 2, 3 and 4 which show spines and figure 5 which demonstrates folds in an egg shell will show this distinctly enough. No folds in any shell could be found

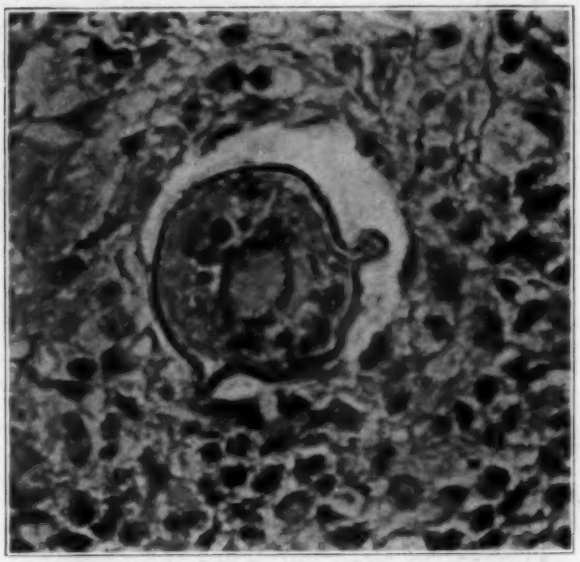

Fig. 5.—Folds in shrunken egg shell; they look wholly different from spines and can hardly be mistaken for such.

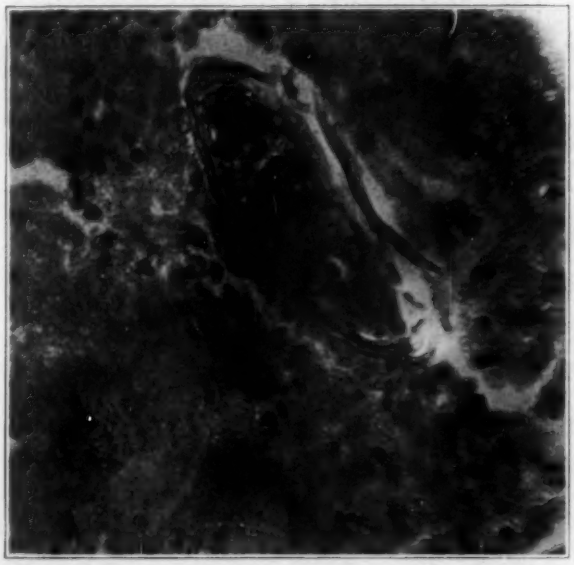

Fig. 6.—Miracidium-like larval stage in broken shell. The spine is not visible in this picture. The egg is situated in the lumen of the appendix; it is surrounded by fecal material.

which bore a closer resemblance to a spine than the one did which is shown in figure 5. The spines remain fixed in the surrounding tissue even when the whole egg is separated from it by artificial shrinking. Folds of the shell are never so sharp as the spines are. The fold includes the whole thickness of the shell, while the spine at its base is separated from the inner layers of the shell by a fine line which is concave inward.

The literature contains reports on "isolated" or "primary" bilharziosis of the appendix. To the discussion of this diagnosis the same considerations apply as to the frequently described cases of "primary" tuberculosis in some organ. Unless complete postmortem examinations

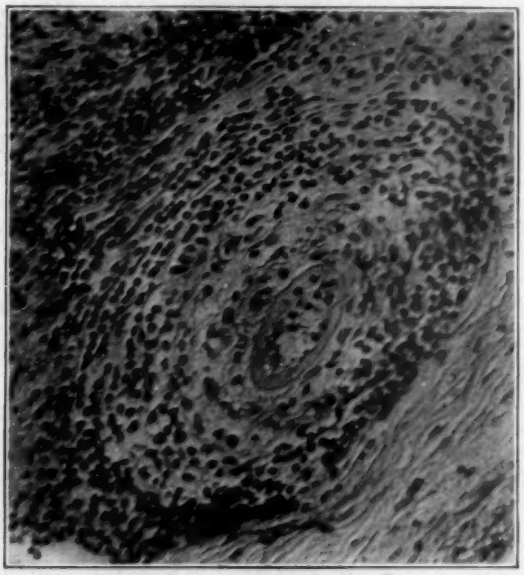

Fig. 7.—Onion shell structure with concentric layers; its center dimly shows the outlines of an egg.

can be obtained with careful microscopic study, the existence of an isolated schistosomiasis of the appendix cannot be accepted. It is highly improbable when one considers the mode of infection in this disease. None of the cases reported in the literature fulfils the requirements necessary for a diagnosis of primary bilharziosis; this applies especially to the case of Burfield.[1] A patient in the Woman's Hospital several years ago had eggs of *Bilharzia* in the appendix. Bayley and Bullard,[2] who published the case, did not find any evidence of further bilharziosis, but the persistent eosinophilia which their patient had is suggestive of

1. Burfield, J., and Shaw, E. H.: Lancet **1**:368, 1906.
2. Bayley, C. H., and Bullard, E. A.: Surg., Gynec. & Obst. **36**:704, 1923.

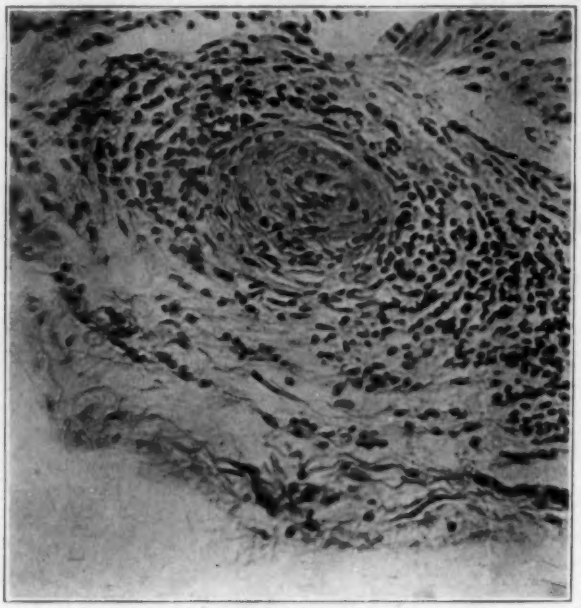

Fig. 8.—Similar formation in more advanced stage.

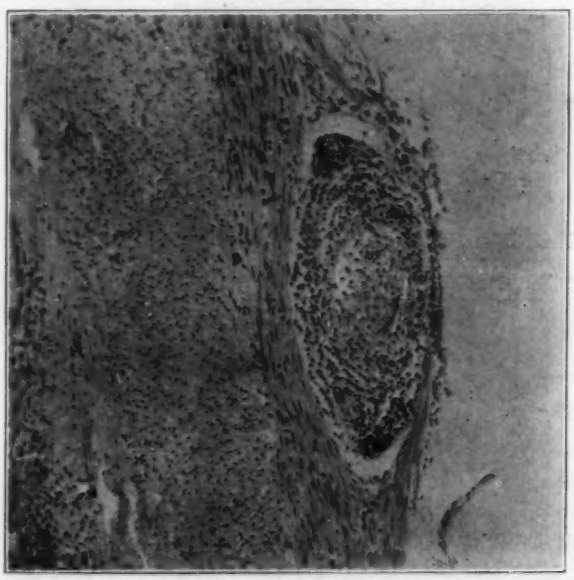

Fig. 9.—Similar formation, situated in the peripheral muscular layers and bulging from the peritoneal surface. Such bulging is obviously large enough to be seen with a hand lens.

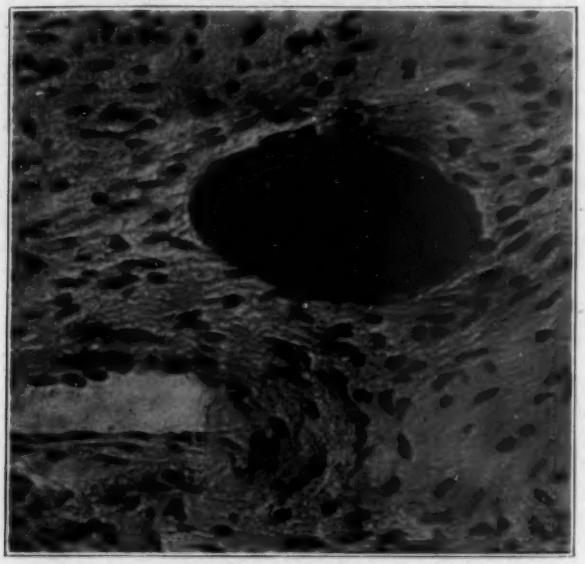

Fig. 10.—Calcified egg in cervix uteri. Note the absence of tissue reaction.

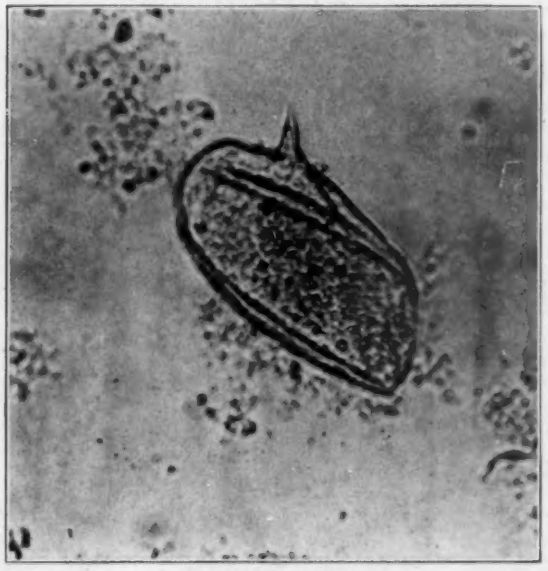

Fig. 11.—Egg from feces; lateral spine, unstained specimen. This picture was taken without color screen while in the others Wratten K2 was used.

other localizations which, as in so many cases, were without symptoms. Looss [3] states that in bilharziosis of the intestine the appendix is frequently involved or in rare cases apparently the appendix alone; but the cases he quotes from the literature are not convincing. The opposite fact, namely, that even in severe intestinal infection the appendix may remain uninvolved, has been proved by Letulle.[4]

In the case presented, as in others, polar and ventral spines have been found, thus disproving the idea of a Manson type of schistosoma, which was believed to be characterized chiefly by the lateral position of the spine. In the sections of the appendix eggs with polar spine and eggs with ventral spine were found very near each other; the other explanation of these findings, that of a double infection with two different varieties of schistosoma, seems far fetched. And it would not explain how the African form with the polar spine came to the West Indies where the patient presented acquired the disease. In the feces only lateral spines were seen, but since only a few eggs could be detected in the feces, no conclusion can be drawn from the absence of eggs with polar spine.

CONCLUSIONS

Severe schistosoma infection in the appendix may be present without any clinical symptoms.

Isolated or primary schistosomiasis of the appendix does not exist; at least it never has been demonstrated in a convincing way.

The position of the spine, whether polar or lateral, does not allow the differentiation of two kinds of schistosoma.

The spines can easily be demonstrated in stained tissue sections.

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3. Looss, Arthur, in Mense: Handbuch der Tropenkrankheiten **2**, 1914.
4. Letulle, Maurice: Le rectum bilharzien, Paris, 1905.

GENERALIZED TORULA MYCOSIS*

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AND
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The history and literature on yeast and pseudoyeast infections in man have been thoroughly reviewed by several authors in the last decade, and especially by Stoddard and Cutler.[1] These authors classified the various yeast infections as those caused by true yeasts, by *Oidium,* by *Coccidioides immitis* and by *Torula.* From all cases with involvement of the central nervous system reported, they selected four which were characterized by their chronicity, the prominence of the nervous symptoms throughout the course of the disease, the typical brain and meningeal lesions and the absence of skin involvement. These four cases they considered true *Torula* infections. They added two of their own cases to this group, and included a study of a culture of *Torula* obtained from Frothingham, who had reported the first *Torula* infection in an animal.[2] Since 1916 six more cases of *Torula* infection have been reported. Ours is the thirteenth case to be recorded and presents certain features that have not been mentioned in the other twelve.

REPORT OF A CASE

History.—A man, aged 54, a Kurd who was admitted to the Cook County Hospital in Dr. Lilly's service with the entrance room diagnosis of meningitis, complained of severe headache and a feeling of intense weakness and chilliness. He came to the United States twenty-one years previously, and had been traveling about from place to place until about two years before. During this last period he had been working as a laborer in Gary and Whiting, Indiana. Further history could not be obtained because of the patient's irritability and refusal to answer inquiries. Later, after investigation in Gary and Whiting, it was learned that in the four to six months before his admission to the hospital, he had been known in the Turkish coffee houses that he frequented as the "man with the headache," so severe and constant was this complaint. For two months previous to his admission he had been confined to bed in a Gary hospital. During this time he had had periods of chilliness and actual chills. The diagnosis at this hospital was meningitis. No spinal puncture was performed.

Examination.—General nutrition was good. The pupils were regular, the left somewhat larger than the right. Their reaction to light was sluggish. There

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*From the department of pathology and bacteriology of the University of Illinois Research and Educational Hospitals, and the department of pathology of the Cook County Hospital.

1. Stoddard and Cutler: Studies of the Rockefeller Institute for Medical Research **25**:1, 1916.

2. Frothingham: J. M. Res. **8**:31, 1902.

was moderate rigidity of the neck. The chest revealed normal resonance and breath sounds. The tendon reflexes were slightly exaggerated, the left more than the right. The Babinski sign was negative; the Kernig sign, bilaterally positive. There was no ankle clonus.

The spinal fluid, on entrance, was uniformly slightly bloody and under moderate tension. Many red blood cells and numerous yeastlike organisms, some budding, were found. Only an occasional large or small lymphocyte was present. No polymorphonuclear leukocytes were found. The diagnosis was coccidioidal meningitis.

Treatment and Course.—The treatment consisted of potassium iodide, 30 grains (1.9 Gm.) three times daily and tartar emetic solution intravenously daily for fourteen days in increasing doses, beginning with 1 cc. of a 1 per cent solution and increasing 1 cc. daily until 7 cc. were given. This drug was discontinued at the end of fourteen days as no benefit was noted.

The patient lost weight and became progressively weaker. The delirium became constant. The temperature, which was 99 F. on entrance, rose to 100 F. the next day and then dropped, staying between 98 and 99 F. with only an occasional rise to 100 F. (R.). During the last week of his illness the temperature was more irregular, rising to 102 on several occasions. The pulse rate in general paralleled the temperature.

An acneform lesion was seen on the patient's forehead on the twenty-sixth day of his illness. From its appearance it must have been present for some time, but because of its close resemblance to an ordinary acne papule it had received no particular attention. The lesion was a pointed, indurated papule with a crusted surface beneath which there was a depression of about 3 mm. in depth. The surface below this crust was clean. The induration did not extend beyond the skin, this being freely movable over the frontal bone. The lesion did not become enlarged during the rest of the course; and no other skin lesions, except typical sacral and ischial decubitus ulcers, were noted.

Laboratory Findings.—Cultures of the spinal fluid (four cultures at intervals of about one week, the first from fluid taken July 1, the day of admission) revealed what was reported as a "torula-like" organism. Four blood cultures were taken at similar intervals, and all contained a similar organism in pure culture.

It is noteworthy, in view of our inability later to isolate this same organism from postmortem cultures, that the last blood culture was taken five hours before death, and that this revealed a growth of the same torula-like organism in pure culture.

Cultures from the right nasopharynx and from the skin lesion described above likewise contained this same organism with no other yeastlike growth. The left nasopharynx, the ears and the urine did not contain any yeastlike organisms.

The Wassermann reaction on the blood and the spinal fluid was negative.

Necropsy.—Necropsy was performed by Dr. D. J. Davis five hours after death.

There was marked emaciation. On the forehead, just to the left of the median line and 2 cm. above the left eyebrow was a round lesion, 1 cm. in diameter, the margins of which were prominent. This was covered by a scab, below which was a red, granular surface. There was no other skin lesion except superficial ulcers over the sacrum and both trochanters. Pyorrhea alveolaris was marked. The inguinal, axillary and supraclavicular glands were distinctly palpable and firm.

On each side of the larynx were enlarged lymph glands containing yellow nodules. There was a large amount of a purulent material on the back wall of the pharynx. The thyroid contained a few colloid cysts. There was no increase in fibrous tissue. The tonsillar crypts were prominent and contained cheesy granules.

The heart weighed 250 Gm. There was some fibrous thickening of the free margins of the mitral valve.

The left lower lobe was large and soggy. The upper lobe was soft and light. Crepitation was feeble in the lower lobe where many palpable nodules from 0.5 to 1 cm. in diameter were present. Some small, gray and brownish red nodules were seen on the cut surface. The upper lobe revealed on its cut surface near the apex, an irregular nodule 1.5 by 2 cm., composed of gray, caseous material surrounded by fibrous tissue. On the right parietal pleura, over the eighth rib, 5

Fig. 1.—Miliary lesion of the bone marrow; × 2.

cm. from the vertebral column, was an elevated, yellowish-gray lobular nodule, 1 cm. across. On section this was fibrous. The right lung had a few fibrous adhesions over the pleura. In the upper lobe was a puckered scar 1 cm. long, which extended for 1 cm. into the lung tissue. In this region caseous material was present in a small cavity which was surrounded by fibrous tissue. There were two other gray, caseous nodules in the upper and middle lobes. On section, the lower lobe revealed an abscess cavity containing a pinkish putrid substance. This cavity was 6 cm. long and 4 cm. wide. The wall was irregularly roughened, and composed of fibrous tissue. A cavity about one-half the size of the one described was present in the upper part of the right lower lobe. Its contents and structure were similar to the first. The peribronchial lymph glands were large, anthracotic and contained gray fibrous areas.

The appendix was enclosed in a fibrous pocket. It lay behind the ileum and was directed posteriorly. It was funnel-shaped and 7 cm. long. The spleen weighed 115 Gm. Its capsule was wrinkled. A few small gray nodules were present in its substance. The liver was soft, its capsule thickened. The abdominal and thoracic aorta revealed only a few small areas of sclerosis. The stomach had punctiform submucous hemorrhages. The pancreas was normal. The right kidney was very soft and grayish red on section. Miliary abscess-like bodies were present in the cortex and medulla. The markings were indistinct. The capsule stripped easily. The mucosa was slightly granular and was covered by a small amount of grayish-white, purulent material. At the lower pole of the kidney there was a small, gray, firm tumor mass, 1 cm. across, pedunculated and adherent to the

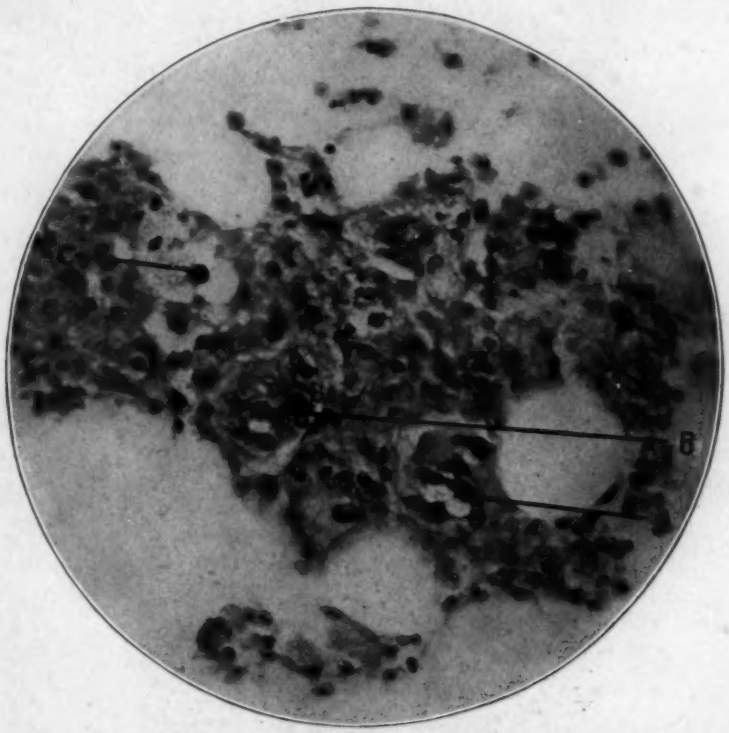

Fig. 2.—Lesion of the bone marrow of femur; *A* indicates group of budding torulae; *B*, group of torulae with spicule-like projections from the periphery of same; *C*, solitary torula; × 250.

capsule and kidney substance. It was firm and fibrous on section. The left kidney was the same size as the right. The capsule was adherent in places. Under it were uniformly scattered small, yellowish-white abscesses. These were also seen on the cut surface both in the cortex and in the medulla. In the latter they tended to become linear in arrangement. The cortical markings were obscure. The kidney substance was friable. The pelvis contained a small amount of purulent material, and its mucosa was granular. The kidneys together weighed 400 Gm.

The bladder was distended with purulent urine. Its mucosa was everywhere hyperemic.

There was a moderate increase in the spinal fluid, which was milky. The brain was flabby, dull and turbid. An exudate was uniformly distributed over the base and vertex. Small, gray, tubercle-like bodies were seen in the sulci, quite abundant in the region of the sylvian fissure. The optic chiasm was embedded in organized adhesions. The dura was unaltered. The left sphenoidal sinus contained a purulent exudate.

The formalin hardened brain is described by Dr. G. B. Hassin as follows: There were no abnormalities of the base of the brain. The meninges over the convexity were opaque, especially over the frontal and parietal lobes. The convolutions were practically of normal size, the sulci unaltered. The right parietal lobe revealed subpial hemorrhages confined to the inner surface. The lateral

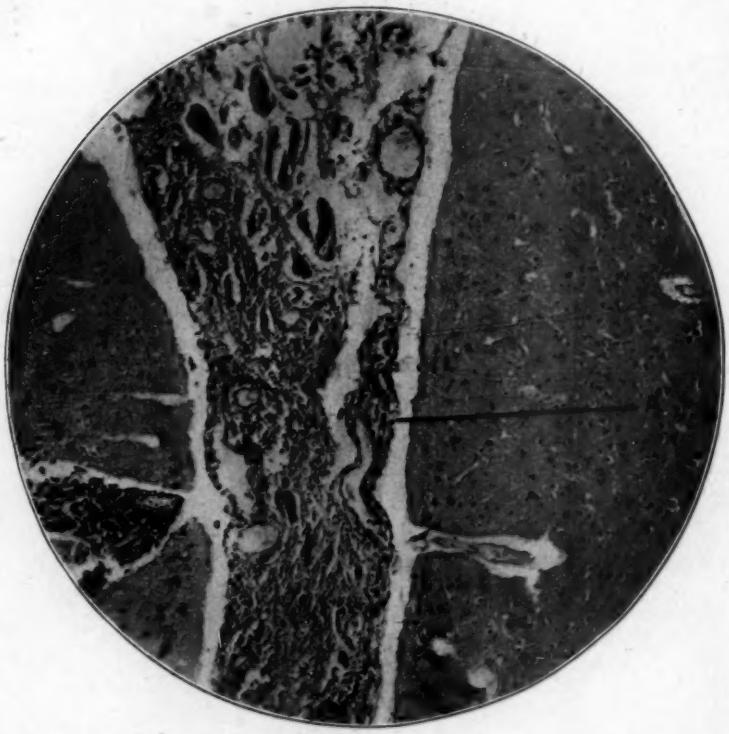

Fig. 3.—Torula leptomeningitis. Intracerebral lesion opening into subarachnoid space; *A*, organisms in meninges; ×75.

ventricles were slightly dilated and filled with a gelatinous mass. The third ventricle was slightly dilated and empty. The gray matter was sharply demarcated from the white substance. Coronal sections through the occipital lobe revealed no abnormalities. Coronal sections through the parietal lobes revealed numerous areas of softening, varying from 2 by 1 cm. to several millimeters in size, located in the gray matter and putamen on both sides. They were present also in smaller numbers in the subcortical substance of the frontal lobe. They were sharply demarcated from the surrounding brain substance and had the "soap-bubble" appearance described by Freeman and Weidman[3] in their case.

3. Freeman and Weidman: Arch. Neurol. & Psychiat. **9**:589, 1923.

The bone marrow of the right femur contained a large amount of red material mixed with the yellow. There was a clear, gelatinous material present in large amounts. In it were found round, gray bodies (fig. 1) about 1 mm. in size. Where these were most numerous the bone marrow was grayish-green.

Microscopic Examination.—Through Dr. E. R. LeCount we early obtained microscopic sections stained with hematoxylin and eosin, phosphotungstic acid and hematoxylin, and with Mallory's connective tissue stain. In addition we used a Gram stain with lithium carbonate as a counterstain, a methylene blue and eosin stain and a toluidin blue stain. Of the stains used, the last three were most satisfactory. Gram's method was used to bring out the organisms, disregarding the

Fig. 4.—Intracerebral lesion, early type; *A*, organism with a wide clear peripheral zone; *B*, organism with a narrow clear peripheral zone; × 140.

tissue changes, while the stains with methylene and toluidin blue were found to be the most satisfactory both for organism and tissue study. With the latter the organisms stain more intensely than either lymphocytes or tissue cells, and may be recognized even with the low power lens. The morphology of the organisms has been carefully studied by Stoddard and Cutler [3] and more recently by Sheppe.[4]

In this case, as in others, budding forms from 3 to 15 microns in size were present. No endospores were noted.

4. Sheppe: Am. J. M. Sc. **167**:91, 1924.

Sections were made from the abscesses of the right lower lobe. At the edge of the abscess the alveoli were filled with a homogeneous staining material containing here and there a few pyknotic nuclei and very many round, deeply staining yeast bodies, with spicule-like processes extending from their periphery. Many nuclear remnants, plasma cells, round cells and old fibrin were present here. In some places large protoplasmic masses containing one or two poorly staining, spindle shaped nuclei and from 2 to 6 or more organisms were present. Farther away, about 0.5 cm. from the abscess cavity, the reaction was less marked. Here were found typical foreign body giant cells containing yeastlike organisms, about which there was a clear zone. Fibrosis and hyaline changes were found in other sections taken at a distance from the lung abscess. In these the organisms were few, occurring singly or in groups of two or three.

Fig. 5.—Glomerulus partially replaced by organisms; *A*, chainlike budding form resembling a mycelium; *B*, organisms within the remains of a glomerulus; ×250.

The right upper lobe revealed fibrocaseous tuberculous changes. Tubercle bacilli in large numbers were found in the caseous area of one section. No *torulae* were found in this or in any of the other sections revealing tuberculous changes.

Sections taken from the nodules found in the lower lobe (fig. 6) revealed changes similar to those noted in some of the sections taken 0.5 cm. away from the edge of the abscess in the right lower lobe. The alveoli were filled with fibrin, round cells, plasma and giant cells. Within the giant cells yeastlike bodies each surrounded by a clear zone were found. These were also found outside of cells,

occurring in groups with spicule-like processes protruding from the periphery of each organism. The clear zone previously noted was present here also about many of the organisms. No evidence of tuberculous changes was found in these nodules.

Sections of the brain were stained with hematoxylin and eosin, toluidin blue, and Alzheimer's stain. The two latter were the most satisfactory both for the histologic and morphologic study of the organisms.

The leptomeninges (fig. 3) were greatly thickened, and infiltrated with many round or oval, doubly refractile bodies, many of which were budding. A large number of these lay within irregular, protoplasmic masses, some of which contained several nuclei. About each organism or group of organisms within these

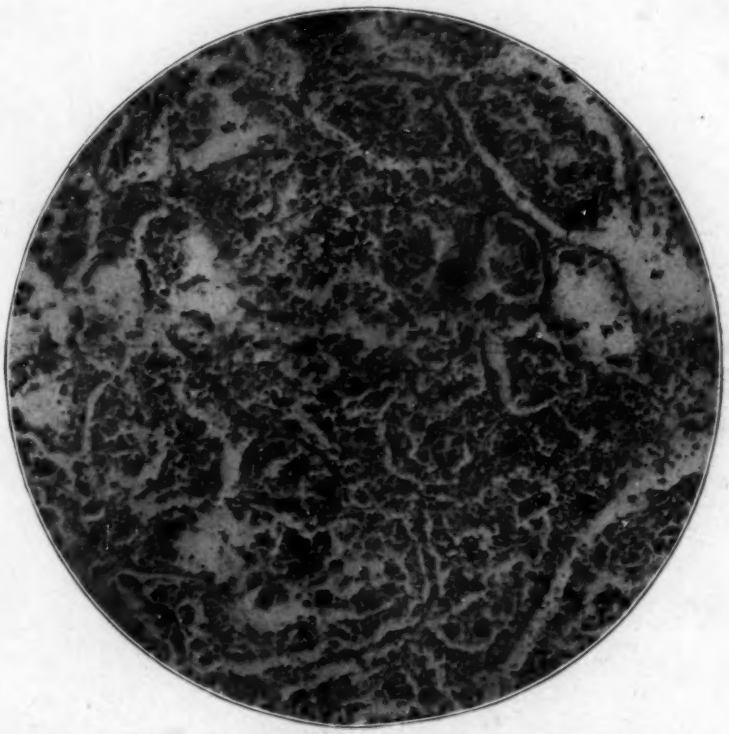

Fig. 6.—Section from nodule in the left lower pulmonary lobe (bronchopneumonia). The deeply staining round bodies are torulae; × 90.

giant cells was a clear space varying in width from a very narrow strip to a zone wider than the organism. In some this nonstaining area about the organisms occupied practically the entire cell, leaving only its border to mark the structure. Many round and plasma cells were also present, but no polymorphonuclear leukocytes.

The changes in the brain itself were particularly striking in contrast to those found in the meninges. The intracerebral lesions, while differing in the degree of advancement, were nearly all characterized by the absence of any inflammatory reaction. Those least advanced consisted of sharply demarcated areas, most of them round or oval, varying in diameter from 50 to 300 microns (fig. 4). The

borders of these lesions were smooth. There was no evidence of compression of glial fibers at the periphery. The glial cells within the sharply demarcated areas stained more deeply than those of the surrounding brain tissue, the cell borders were less distinct, and the nuclei of some fragmented. Relatively few organisms were present in such early lesions, and about each organism there was a distinct, clear zone. The resemblance of these areas to focal softening resulting from vascular obstruction was striking. There were, however, a large number of these lesions containing a central blood vessel the lumen of which was not obstructed. No inflammatory cells were present either about or within this type of lesion.

In a more advanced type of change the area of destruction was wider, more diffuse and no longer oval or circular. The number of organisms was greater,

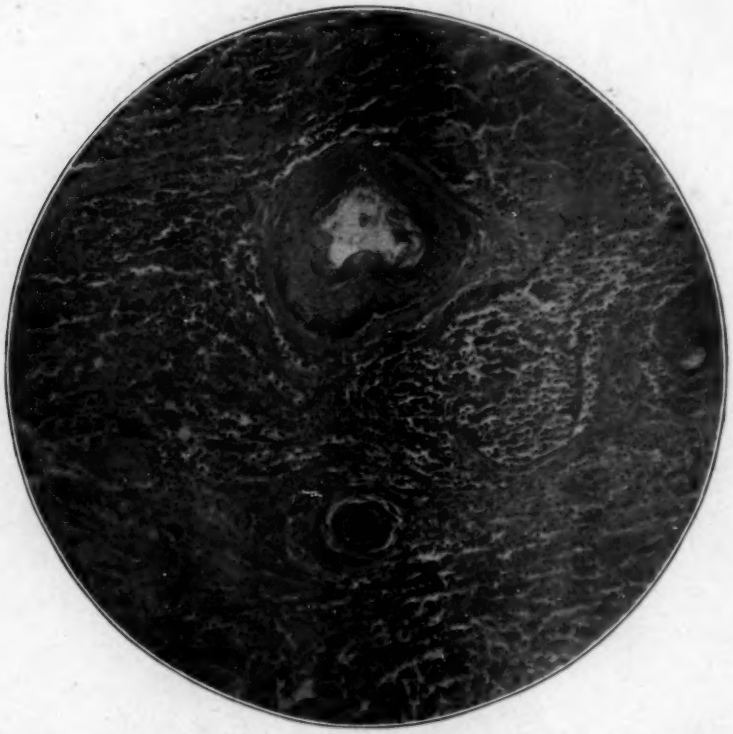

Fig. 7.—Cross section of skin. Marked infiltration of corium with organisms. An occasional organism is present in the epidermis; × 100.

while the cell débris was decreased in amount. A few of the lesions in this stage revealed evidence of compression of the bordering glial fibers. Further suggestion of mechanical pressure was found in a few of the lesions bordering the lateral ventricle. The ependyma was bulged inward toward the lateral ventricle, and had apparently been ruptured in several places by the expansion that had taken place. Here the organisms were found in masses within the lateral ventricles and about the choroid plexus. Although, as previously stated, there was no reaction about the majority of the intracerebral lesions, yet there were a few areas about dilated vessels which differed from those described. Such a

lesion is characterized by a marked round cell infiltration about the periphery of a blood vessel and the presence of relatively few organisms.

Sections of the cord and medulla revealed no changes either in the meninges or in the nerve tissues.

In the kidneys there was marked generalized infiltration of the interstitial tissue with round cells. Some of the tubules were filled with round and budding organisms from the periphery of which numerous spicules protruded. An occasional cell lining a collecting tubule was replaced by an organism. The tubule wall was completely eroded in some places without any dilatation of the lumen, and with no evidence of compression of the cells of the opposite wall. Organ-

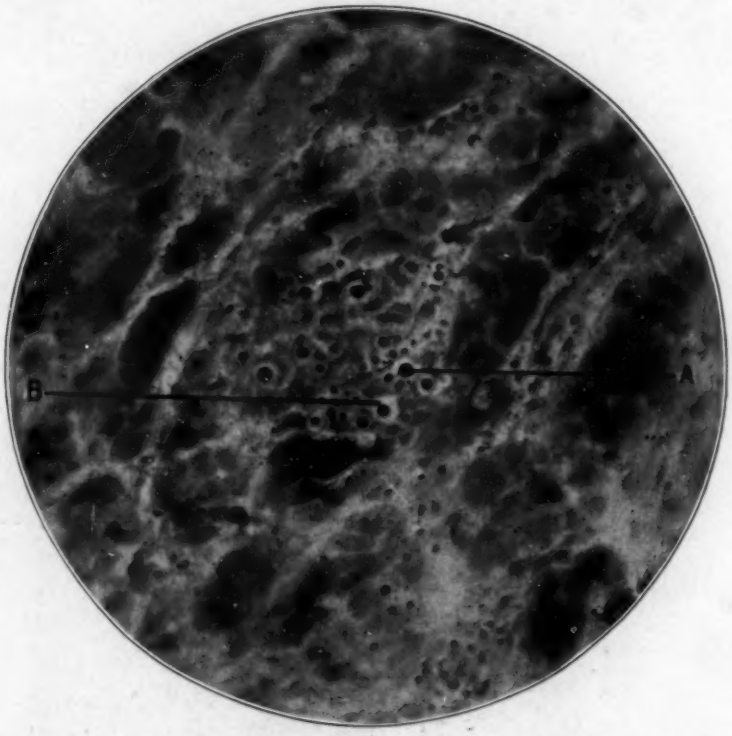

Fig. 8.—Small lesion of suprarenal. Note clear zone about each organism, as in *B*; *A*, budding torula; × 250.

isms were more numerous in the glomeruli. One such structure (fig. 5) was almost completely replaced by a mass of organisms. A mass of débris in which organisms were numerous and nuclear remnants recognizable was present in this area of focal necrosis. About each lesion was a marked round cell infiltration, but no polymorphonuclear leukocytes were found. Several areas revealed giant cells in which the organisms were found. The mode of dissemination was indicated here as in other places by the presence of organisms within the blood and lymph vessels as well as in the kidney parenchyma. The tumor nodule in the right kidney consisted of whorls of fibrous tissue.

The suprarenals (fig. 8) contained lesions almost similar to those noted in the kidneys. There were circumscribed, oval or round, large and small areas of

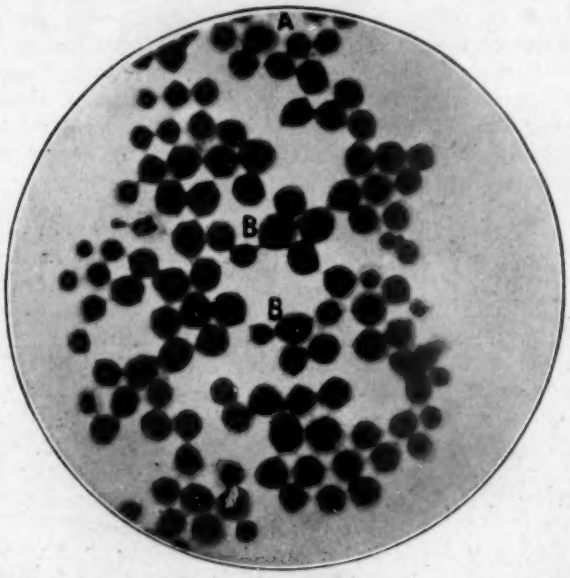

Fig. 9.—Torula histolytica, seven day culture; *A*, beginning of capsule; *B*, budling forms; × 1200.

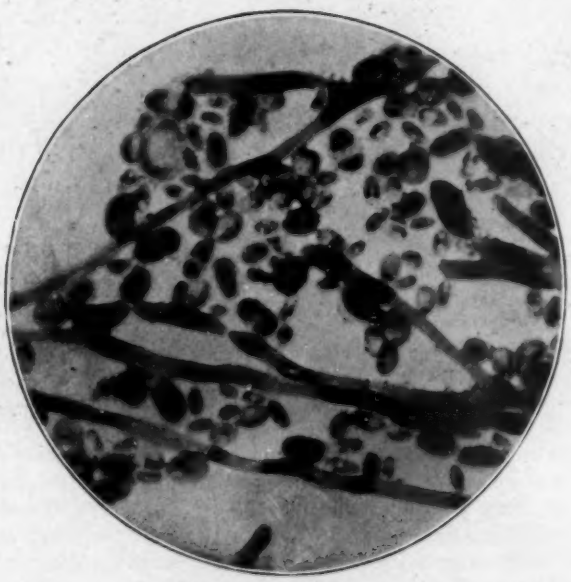

Fig. 10.—Oidia from seven day culture; × 1200.

necrosis in which numerous yeastlike organisms were found, many within vacuolated suprarenal cells. A few fibroblasts and some round cells were present. Some of the fibroblasts surrounded individual organisms. No reaction was present in the suprarenal tissue at the periphery of the lesions.

In the thyroid there were numerous extensive areas of hyaline fibrosis with little colloid material in these areas. There were groups of budding organisms in clear spaces surrounded by colloid or hyalinized material. Masses of round cells were present in a few places in this hyalinized tissue.

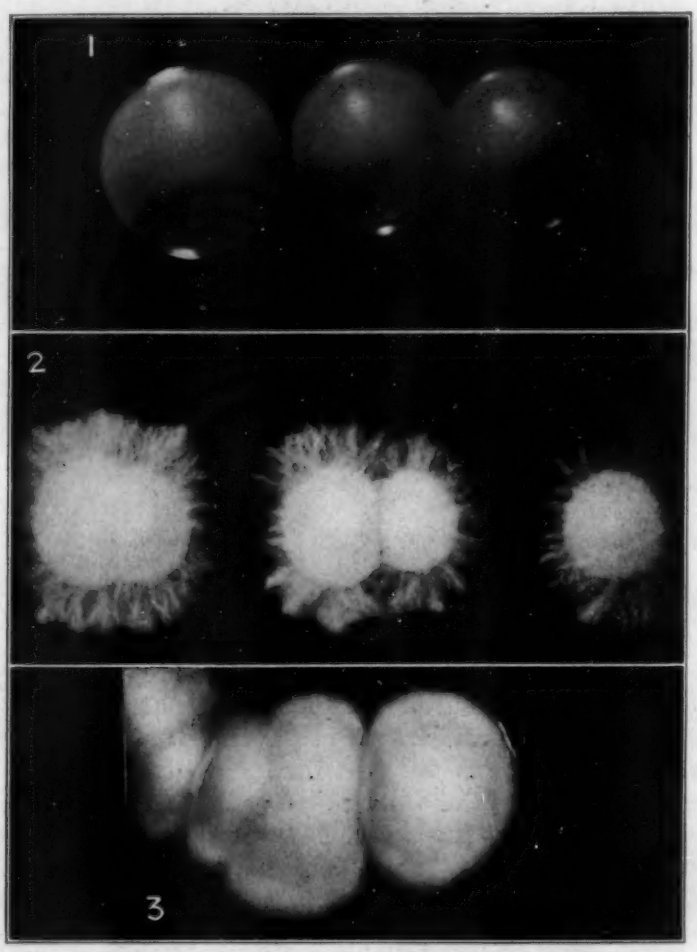

Fig. 11.—*1*, colonies of torula histolytica; × 7; *2* and *3*, oidium colonies; × 7.

The normal structure of the bone marrow of the femur was replaced over large areas by a hyalinized, poorly cellular, fibrous tissue infiltrated in some places by round cells. Only one group of organisms could be found in the sections studied (fig. 2). These were gathered in clumps surrounded by many round and a few elongated cells resembling epithelioid cells. Microscopic study made by crushing the grayish-white punctiform areas described in the necropsy report revealed a few bodies having the staining properties of *Torulae*, and a few lymphocytes.

With the Gram stain the skin lesion revealed a tremendous number of round or oval organisms as well as many budding forms (fig. 7). Only two or three areas of intracutaneous inclusions of the organisms were found. These were in the deepest layers of the stratum corneum and seemed to be invasions from the greatly infiltrated corium. It was only with this special stain for the organisms that their presence intracutaneously could be noted. No giant cells, round cells or polymorphonuclear cells were present about the organisms within the epidermis. With the other stains used an extensive, heaped up ulcer was seen, the surface covered with old fibrin. The entire corium of the ulcer region was almost entirely filled with the organisms, diffusely spread except in a few areas where they were grouped in clumps. About these organisms was a granular débris; where they occurred in clumps there was a clear area about them. Under the intact skin at one margin of the ulcer there was a marked, diffuse infiltration of the yeastlike organisms in a granular débris. Some round cells and many fibroblasts were present. The latter in many places revealed a peculiar arrangement, three to four of the cells surrounding one organism about which there was a clear space, giving the appearance of an organism within a capillary. Another type of lesion found in the areolar tissue consists of a sharply demarcated, oval area occupying about one-fifth of a high power field. This was made up of granular débris, a few oval and elongated nuclei and many doubly refractile organisms, some of which were surrounded by a ring of fibroblasts like that described. Organisms were also found in two places within the lumina of lymph vessels. The area at one side of the skin lesion revealed an increased number of fibroblasts, but was otherwise free from evidence of inflammatory reaction.

The nodule found on the right parietal pleura consisted of highly vascular fibrous tissue in which there were many giant cells, with typical tubercle formation about some.

The cervical lymph glands revealed fibrous and caseous tuberculous changes. No yeastlike organisms were present.

MICROBIOLOGY

It has been mentioned previously that before death pure cultures of *Torula* were isolated from the spinal fluid and blood repeatedly, from the latter as late as five hours before death. Positive cultures were likewise obtained from the right nasopharynx and facial lesion. It was therefore somewhat of a surprise to find after death instead of *Torula,* oidium-like organisms and a bacillus of the *B. coli* group in the blood, the spinal fluid, the pus from the left sphenoid sinus, the right temporal fossa, the suprarenals, the abscess of the right lower pulmonary lobe and the bone marrow. A number of smears made at necropsy from these regions revealed some organisms that morphologically resembled *Torula* and others that resembled the oidia. Repeated attempts were made to isolate organisms similar to those obtained before death by cultivating and subcultivating in various dilutions on a variety of mediums and under various p_H concentrations. About 150 plates were made without success. The oidia cultivated consisted of two distinct strains. One produced a dry coherent growth, while the other produced slightly elevated, dry, white colonies.

In seeking an explanation for this, two possibilities presented themselves: first, that the postmortem strains were mutants of the antemortem ones; and second, that the postmortem outgrew the antemortem organisms.

Two series of experiments were started in vivo as well as in vitro to determine whether either or both suppositions were true. The first series of experiments consisted in growing *Torula histolytica* under varying conditions: incubator, room temperature, at 20 C., aerobically, anaerobically, and under partial oxygen tension; on various mediums, dry, moist, solid, and in liquid; acid, alkaline, and neutral, carbohydrate, plain, blood, and in gelatin for as long as three months but without any change.

A second series of experiments consisted of inoculating six guinea-pigs intraperitoneally: two with *Torula histolytica,* two with *Oidium,* and two with equal amounts of the two cultures.

From forty-eight to seventy-two hours after inoculation, one set of three pigs received each intraperitoneally 2 cc. salt suspension of a twenty-four hour agar culture of *B. coli* (the strain isolated from the patient postmortem). Twenty-four hours after inoculation the pigs that were not dead were killed, smears and cultures were made from all organs, including the brain, on blood agar, Endo's medium and on neutral 1 per cent dextrose agar. The results revealed the fact that *Oidium* outgrew *Torula histolytica,* so that the latter could not be isolated culturally, although the organism appeared on smears. *B. coli* did not interfere with the growth of either strain.

Similar experiments were run in vitro. Nine test tubes of dextrose broth were inoculated as follows: tube 1, *Torula histolytica;* tube 2, *Torula histolytica* and one strain of *Oidium;* tube 3, the same as 2 plus *B. coli;* tube 4, *Torula histolytica* plus the second strain of *Oidium;* tube 5, the same as 4 plus *B. coli;* tube 6, one of the oidia; tube 7, the same as 6 plus *B. coli;* tube 8, with the second strain of *Oidium;* tube 9 the same as 8 plus *B. coli.* These were plated on 1 per cent dextrose neutral agar and also on 1 per cent dextrose and 1 per cent hydrochloric acid agar immediately and every three to four days for a month and a half. The results observed were that every postmortem strain outgrew the antemortem one. The presence of *B. coli* did not hinder the growth of either strain. This, then, may be considered a possible explanation for the failure to isolate *Torula* in postmortem cultures. The presence of *Oidia* is not satisfactorily explained. They might have been present locally in one of the lesions, as the lung abscess, and they may have been disseminated as an agonal spread or in taking the cultures.

Morphology.—Torula histolytica is a round, double-walled organism, enveloped by a transparent, slightly refractile, gelatinous capsule which

holds the organisms together. This capsule appears large and distinct in smears from tissue and from old cultures. In young cultures these organisms stain evenly dark, while in old cultures there is a differentiation into light staining cytoplasm and dark staining granules. *Torula histolytica* reproduces by budding, and does not produce mycelia even under the most unfavorable conditions.

Oidia are oval, more or less elongated, fail to reveal any definite capsule and bud in tissues. Occasionally several buds attached together give the appearance of a short mycelium. Mycelia are produced in culture.

Staining Characteristics.—Torulae are gram-positive when young and gram-amphophil when old. They stain well with Loeffler's methylene blue, toluidin blue and with Wright's stain. The two latter are especially good, bringing out the chromatin granules, while toluidin and methylene blue bring out the capsule very well.

Cultural Characteristics.—Torula grows as well at room as at incubator temperature, with a wide range of p_H values. It produces yellowish white, smooth, circular, elevated colonies which become yellow and finally brown with age. Growth is best on solid carbohydrate medium. In liquid medium the organisms settle to the bottom.

Oidium produces white, dry or slightly moist, flat or somewhat elevated colonies with mycelia extending along the medium. In liquid medium a heavy pellicle is formed which adheres to the sides of the tube. On potato growth is luxuriant. Milk is not changed. Gelatin, both plain and dextrose, is not liquefied.

All of the carbohydrate medium was prepared from sugar-free broth, using 1 per cent sugars in Dunham's fermentation tubes. Andrade's and brom cresol purple were used as indicators. Among the carbohydrates that were used are dextrose, lactose, saccharose, maltose, mannite, insulin, salicin, levulose, raffinose, galactose, dextrin, dulcitol and xylose. The torulae produced no change in any of the carbohydrates, while most of the oidia produced a slight amount of acid in saccharose. One strain also produced a slight amount of acid in dextrose, but gas was not produced in any of the sugars.

Growth is best under aerobic conditions. Anaerobically growth is meager and atypical, *Torula* failing to produce any pigment. All of the organisms grow well under partial oxygen tension. This condition also enhances the growth of mycelia in oidium cultures.

Sheppe,[4] Weis,[5] and Stoddard and Cutler grew *Torula histolytica* on gypsum blocks at 0 to 45 C. for from six to nine months, examining after twenty-four hours and at various other intervals without finding spores.

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5. Weis: Jour. M. Res. **7**:280, 1902.

Immunity Experiments.—Complement-fixation and agglutination tests were made on the patient's serum and spinal fluid. Agglutination was observed only in dilutions of 1 : 40, while complement fixation was slightly positive and only with spinal fluid.

Rabbits and guinea-pigs were immunized with *Torula histolytica* and with the two strains of *Oidium.* The rabbits were inoculated intravenously and the guinea-pigs intraperitoneally. Since *Torula histolytica* was found to be pathogenic for guinea-pigs and rabbits, it was decided to immunize all animals, beginning with a small dose of killed cultures and increasing it as follows: 0.5 cc., 1 cc., 1.5 cc., 2 cc., 2.5 cc. and 3 cc. at weekly intervals; then live cultures were given: 0.5 cc., 1 cc., 1.5 cc., 2 cc., 2.5 cc., 3 cc., and 3.5 cc., at weekly intervals at first and later twice a week.

Nine days after the last inoculation, the animals were starved for fifteen hours and bled from the heart. Various methods—skin tests, precipitin, agglutination, absorption and complement-fixation tests were used in determining the immunity.

Precipitation Tests.—A number of methods were tried. Clear supernatant fluid of forty-eight hour broth cultures and the supernatant centrifuged saline suspensions of organisms boiled from five to ten minutes were used, but without success.

Agglutination Tests.—Agglutination tests were made with heterologous as well as homologous strains, using saline suspensions of forty-eight hour dextrose agar cultures in the usual manner. Readings were made after incubation periods of two and nine hours, at 37.5 C. dry heat, and again after remaining in the icebox over night.

Torula histolytica immune serum showed agglutination only in dilutions of 1 : 80. While the serum showed only feeble agglutination with the homologous strain, it showed strong cross-agglutination in dilutions as high as 1 : 1,280 with heterologous organisms (guinea-pig serum 1 : 320 and rabbit serum 1 : 1,280). Controls with normal guinea-pig and rabbit serum were negative.

Absorption Tests.—Absorption tests were made using serum dilutions 1 : 10 with heavy saline suspensions of homologous as well as heterologous strains in respective tubes, incubating at 55 C. water bath for two hours, placing in the icebox over night, centrifuging, and using the supernatant fluid for agglutination as above. The results show that while there is absorption with homologous strains, there is also absorption with the heterologous strains.

Complement-Fixation Tests.—A number of different antigens were prepared: (*a*) Alcoholic extract of dried organisms failed to show any antigenic properties. (*b*) An antigen of the strain obtained from the antemortem blood culture was prepared in the following manner: A

heavy suspension of the organisms in sterile distilled water was broken by alternate freezing and thawing about twenty times, liquid air being used for freezing and hot water for thawing. Cultures were made to determine sterility. Organisms remaining alive were killed by saturating with chloroform which was later evaporated. The material was centrifuged and enough sterile salt added to the supernatant fluid to make it isotonic. This was the stock antigen.

Another antigen, using the spinal fluid postmortem strain, was prepared as above, but the organisms were broken in a ball grinding machine. This antigen was used in dilutions of 1 : 10.

A fourth antigen, using the strain from the suprarenal, was prepared by making a heavy suspension in salt solution, breaking the organisms in a sterile mortar in sea sand. The sterile supernatant fluid was used. All antigens were titrated, using the respective immune serum for the positive serum and salt solution for the negative. One half of the anticomplementary dose was used in the test, using two units of complement, two units of amboceptor and sensitized sheep cells. Homologous as well as heterologous antigens were used. Normal guinea-pig and rabbit serums were used as controls.

The results show that complete or practically complete inhibition of hemolysis took place with homologous antigen, while complete or practically complete hemolysis took place with heterologous antigens. One of the guinea-pig serums (antemortem strain) failed to give results with any of the antigens. Normal guinea-pig and rabbit serums gave complete hemolysis with all antigens.

Skin Sensitization Tests.—Rabbits, guinea-pigs and rats immunized against the torula and oidium strains were used for this test. One of the antigens used in the complement-fixation experiments (ground organisms) was inoculated intracutaneously. Negative results were obtained, no specific skin reaction being present either in those animals immunized against *Torulae* or against *Oidia.*

Pathogenicity Experiments.—Brewer and Wood[6] report the only case of torula infection in man in which the patient recovered. Rabinowitsch,[7] working with forty strains isolated from various sources in nature, found only eight to be pathogenic. Various workers found that among experimental animals white mice and rats were most susceptible, developing lesions comparable to those in man. Next to these in susceptibility were rabbits which developed lesions in the central nervous system, death occurring three to four weeks after inoculation. Dogs and guinea-pigs were fairly resistant.

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6. Brewer and Wood: Ann. Surg. **48**:889, 1908.
7. Rabinowitsch: Ztschr. f. Hyg. **21**:11, 1895.

In our work guinea-pigs, white mice, white rats and rabbits were used. A 2 per cent saline suspension of forty-eight hour dextrose agar cultures was used, the rabbits being inoculated intravenously and the other animals intraperitoneally. The following doses were given: rabbits 4 cc., guinea-pigs and white rats 3 cc. each and white mice 2 cc.

Torula histolytica proved to be pathogenic for all animals tested. The guinea-pig died four days after inoculation, the white mouse in eight days, the rat in ten days and the rabbit in twenty-nine days. At necropsy these animals showed gray, sticky, fibrinous exudates in the peritoneal as well as in the pericardial cavities, and miliary nodules in the liver, spleen and kidneys. The rat also showed nodules in the lung.

Oidia, on the other hand, were not so pathogenic for the animals tried. The mouse died eleven days after inoculation, the guinea-pig forty-six days, the rat two months and the rabbit more than three months after inoculation. No gross pathology was found except in the guinea-pig, which showed nodules of the spleen and liver.

Microscopically, the experimental lesions due to *Torula* were in all respects similar to those found at human necropsy. There was marked infiltration of the meninges, with giant, plasma and round cells, but no polymorphonuclear leukocytes. Many torulae were present in the meninges. The brain showed lesions similar to those found in man, while the other organs were characterized by like lesions, the huge number of organisms present in clear, apparently dissolved areas, and the absence, or slightness of the cellular reaction being the outstanding features as in man.

The animals infected with *Oidia* revealed no typical lesions with the exception of the one guinea-pig noted. The nodules in the liver and spleen revealed a few yeastlike organisms and many polymorphonuclear cells.

SUMMARY AND DISCUSSION OF THE PATHOLOGIC CHANGES

The essential findings as described consist of one large chronic abscess in the right lower lobe, several smaller abscesses in the rest of the lung, together with nodules in both lungs resembling grossly those of bronchopneumonia. These lesions reveal microscopically a chronic inflammatory reaction of round and giant cells and the presence of a large number of yeastlike organisms—a torula bronchopneumonia. Although superficially the lung abscesses resemble those of tuberculosis, closer study fails to reveal the presence of marked fibrous reaction or of tubercles about the margins of the cavities. Microscopically no relationship can be demonstrated between the tuberculous changes present in the apexes and the changes in the lower lobes The relationship of the suppurative sphenoidal sinusitis, in the pus of which budding

yeast forms as well as a mixed flora of organisms were found, to the pulmonary infection is undetermined. The changes in the other organs are compatible only with a pyemic process, the multiple miliary abscesses of the kidneys, suprarenals and bone marrow, the meningo-encephalitis, the thyroid involvement and finally the lesion of the forehead. Neither the spleen, the liver, nor the other organs revealed any lesions.

The presence of the skin lesion in this case, together with the widespread nature of the infection, makes it necessary to differentiate the condition from other yeast and pseudo-yeast infections, especially from those produced by *Oidia*. This last is made all the more difficult and necessary because of the presence of two oidium-like strains in our various postmortem cultures and the absence of *Torula* in any of these cultures.

The differentiation of torula infections from the yeast and pseudo-yeast infections was first emphasized by Stoddard and Cutler [1] in 1916. The six reports following theirs have all coincided in accepting the differential basis established by them. A true torula infection, according to this definition, is characterized clinically by the long duration of the symptoms of meningeal irritation and the chronicity of the course; bacteriologically, by the presence of yeastlike organisms which reproduce only by budding without mycelial or endospore formation, and which do not ferment sugars. Pathologically the characteristics emphasized in these reports are: the chronicity of the meningeal reaction in which many torulae, giant cells, and round cells but no polymorphonuclear cells are found, the circumscribed "lytic" areas in the brain, about which there is little or no reaction, and finally the absence of skin lesions.

One other characteristic which may be accepted from a study of the cases previously reported is the relative limitation of the lesions to a few organs, especially when the widespread nature of a generalized oidiomycosis infection is compared with the pathologic findings in the torula cases reported (see table). There are nine postmortem examinations recorded of the twelve cases previously reported. Eight of these patients had meningeal and intracerebral lesions, while in one case no report of the brain examination is included. In three of the nine cases (Stoddard and Cutler,[1] Rusk,[1] Sheppe [4]) organisms were found in lung lesions. The description of the lung changes given by Sheppe resembles some of those found in our case. Grossly nodules were present, while microscopically many yeastlike cells, giant and plasma cells were found as well as an increase in fibrous tissue. In one case [1] the kidneys were involved. The pyramids in this case were infiltrated with round and plasma cells as well as with yeastlike organisms. In one

case [8] the esophagus had a white coating, the organisms penetrating to the muscularis. In the only case that was not fatal [6] there was an abscess of the spinal muscles in which the organisms were found and a rarefying osteitis of the spine in which no organisms were present. Freeman and Weidman report the finding of organisms in a lymph gland at the head of the pancreas as the only other lesion associated with a

Reported Cases of Torula Infection in Man

Observer	No. of Cases	Locality	Site of Essential Lesion	Other Organs Affected	Associated Lesions	Portal of Entry (Presumable)	Termination
Brewer and Wood	1	.....	Muscles and vertebral column	None	.....	.....	Recovery
Pierson....	1	California	Central nervous system	.....	.....	.....	Fatal
Stoddard and Cutler	2	Florida	Central nervous system	Kidney	Lobar pneumonia, fibrous pulmonary tuberculosis of the spleen	.....	Fatal
		Massachusetts	Central nervous system	Lungs	.....	.....	Fatal
Rusk.....	2	California	Central nervous system	Lungs	.....	.....	Fatal
		California	Central nervous system	Lungs and kidneys	Bronchopneumonia	.....	Fatal
Türck.....	1	Germany	Central nervous system	Esophagus	Ulcerocaseous pulmonary tuberculosis; caseous tuberculosis lymphadenitis	Digestive tract	Fatal
Von Hansemann [11]	1	Germany	Central nervous system	.....	Pulomnary tuberculosis	.....	Fatal
Evans [10]...	2	California	Central nervous system (no necropsies)	No necropsies	.....	.....	Fatal
Freeman and Weidman	1	.....	Central nervous system	Lymph gland of pancreas	.....	Tonsils	Fatal
Sheppe.....	1	Virginia	Meningeal symptoms (brain not examined) lung		Tonsillitis	Tonsils?	Fatal
Rappaport and Kaplan	1	Indiana	Central nervous system and lung	Sphenoid sinus; kidneys; suprarenals; bone marrow; thyroid skin	Pulmonary tuberculosis; caseous tuberculosis of the cervical lymph glands	Respiratory	Fatal

meningitis and encephalitis. The conclusion based on these findings is that involvement of the central nervous system is present in all cases (meningeal symptoms are present in all), and that very few other organs are involved. Our case differs from the other cases reported not only in the widespread nature of the condition, so that it suggests a septicemia, but also in the presence of a skin lesion from which *Torulae*

8. Türck: Arch. f. klin. Med. **90**:1335, 1907.

were isolated. Furthermore, microscopically this lesion does not resemble that due to *Oidia,* that is, blastomycosis dermatitis. No typical intradermal abscesses were present, no giant cells or polymorphonuclear leukocytes. The organisms were present in enormous numbers in the corium and involved the epidermis only slightly. The reaction about them was chronic, cells closely resembling epithelioid cells surrounding some of the organisms. This may be considered a distinctive skin lesion whose presence adds to the difficulties of the clinical differentiation of a generalized torula mycosis from that of a generalized oidiomycosis.

The slightness and chronicity of the reaction against the invasion of the organism is characteristic of this as of previous cases. The presence of a clear space about the periphery of the individual and about groups of organisms was first pointed out by Stoddard and Cutler.[1] The organism, they suggested, had a lytic property. The possibility of mechanical separation of the tissue by the multiplication of the organism and the secretion of a gelatinous material about them, they considered as a less likely cause for the changes, especially those in the brain. Here they were unable to demonstrate compression of the glial fibers about the periphery of the cystic lesions. Because of these views they named the organism *Torula histolytica.* In their recently reported case, Freeman and Weidman[8] differ with these workers, considering the cerebral lesions mechanical in origin. The lesions described in their report were surrounded by compressed glial fibers. In this case only a few of the intracerebral lesions revealed evidence of peripheral compression. Moreover, there are some characteristic places in the other organs, as in the kidney, in which a definite invasive activity of the organism is evidenced. It seems possible that the lesions are due to both mechanical and chemical forces. The presence of a lytic property, however, has not been satisfactorily demonstrated.

Portal of Entry.—The original focus has in most cases been considered to be located in the lung. In Türck's case[6] the esophagus was considered the portal of entry. Freeman and Weidman[8] considered not only the respiratory tract but more particularly the tonsils as the possible portal of entry. Hranova[9] describes the finding of a nonpathogenic torula in the tonsil of a young girl. Emphasis has been laid on the respiratory tract because of the frequency with which a pulmonary infection is associated with this condition. In three of the cases reported ulcerative pulmonary tuberculosis was present, in one an associated lobar pneumonia, in another a bronchopneumonia, as shown by the accompanying table. The presence of ulcerative pulmonary lesions in our case, together with the findings of ulcerocaseous apical tuberculosis and caseous tuberculous cervical adenitis made it necessary to examine

9. Hranova: Compt. rend. Soc. de biol. **92**:670-672 (March 13) 1925.

the cavities of the right lower and middle lobes and the areas of consolidation for tuberculous change and for the tubercle bacillus, neither of which was found. It may be assumed that the pulmonary infection prepares the soil for torula infection in those cases in which a chronic lung infection is found. There have been, however, a number of cases of torula infection in which no lung changes were noted. This case may be classed with those in which the probable portal of entry is the respiratory tract.

Treatment.—In our case the only treatment consisted of iodides and of tartar emetic solution. Shapiro and Neal [10] used extensive and varied therapeutic measures without altering the course. They report the use of iodides intravenously and by mouth in massive doses, the intravenous injection of a torula vaccine and the intraspinal administrations of colloidal silver without influencing the number of colonies per plate. Intraspinal injections of immunized rabbit's serum was followed by such a severe reaction that it was discontinued after the third dose. The only measure that gave some symptomatic relief was a daily spinal puncture. Except for the surgical treatment that was successful in the one case in which the infection was localized,[6] no treatment has influenced the final fatal termination.

CONCLUSIONS

In this torula infection, the primary lesion was probably in the lung, there being most likely a mixed infection of *Torula histolytica* and an oidium-like organism.

The patient also had tuberculosis involving the apexes of both lungs and of the middle right lobe.

Some months before death *Torula histolytica* became generalized, producing meningitis; or possibly first a sphenoidal sinusitis from which the meningitis developed. This was followed by a generalized torula mycosis involving many organs.

Sometimes during the period five hours before death and five hours after death when the necropsy was performed, *Oidia,* together with *B. coli,* became generalized.

The portal of entrance in this case was in all probability the respiratory tract.

A torula mycosis may be widespread, involving many organs.

Involvement of the skin, while unusual, may occur, this being the first case in which such a lesion has been described.

For the first time definite immunologic reactions were developed in experimental animals, as shown by agglutination, absorption, and complement-fixation tests.

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10. Shapiro, L. L., and Neal, J. B.: Torula Meningitis, Arch. Neurol. & Psychiat. **13**:174 (Feb.) 1925.

INSTANTANEOUS PHOTOMICROGRAPHY OF THE BLOOD PLATELETS

WITH COMMENTS ON THEIR MORPHOLOGY

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One of us [1] has previously reported a study of erythrocytes by means of the ultramicroscope, with dark-field methods. Following the suggestions of Giffin of the Mayo Clinic, we have made certain observations on the blood platelets, which we now report. In the earlier work on erythrocytes it was impossible to obtain satisfactory photomicrographs with less than from five to eight seconds' exposure. However, such exposure is too long, for it permits of too much movement of the cells or platelets under observation and produces, therefore, diffuse or blurred photographic images. Since the chief point to which we wish to call attention has to do with ways and means of obtaining instantaneous photomicrographs, the periods of exposure varying from one-half to one-fifth second, we are giving some details with reference to the experimental set-up, particularly in matters pertaining to the illuminating system.

In figure 1, *1* represents an ordinary type of carbon-arc lantern using carbons from 7 to 8 mm. in diameter. For convenience in directing the light from the arc to the mirror, *m*, of the microscope and thence into the microscope proper, the lantern is placed on an inclined plane which can be varied as desired in its angular position. A water cell, *w*, from 3 to 5 cm. thick, is placed between the arc and the condensing lens, *c*. The condensing lens need be nothing more elaborate or expensive than a reading glass about 10 cm. in diameter and having a focal length of about 25 cm.

The electrical circuit is sketched diagrammatically in figure 2. The source of light is a direct current arc running at approximately 8 amperes during the period of visual observation, and with a suitable resistance arranged in parallel (or multiple) with the fixed resistance so that on the closure of a switch operated by the foot, a current of from 25 to 30 amperes passes through the arc for a brief period while photographs are being taken.

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1. Rockwood, Reed: Physiochemical Aspects of Hemolysis. II. An Ultramicroscopic Study of Hemolysis, J. Lab. & Clin. Med. **10**:19-31, 1924.

We have, in general, obtained the most satisfactory results when using orthochromatic plates or process plates and exposures of from one-fifth to one-half second. The magnification used in obtaining the photomicrographs reproduced in figures 3 and 4 was about 1,900. On account of the movements of the platelets as well as their small size, only two or three of the platelets will be in focus at any given time. The reproductions of the photomicrographs have been retouched so that all of the platelets appear to be in fairly sharp focus.

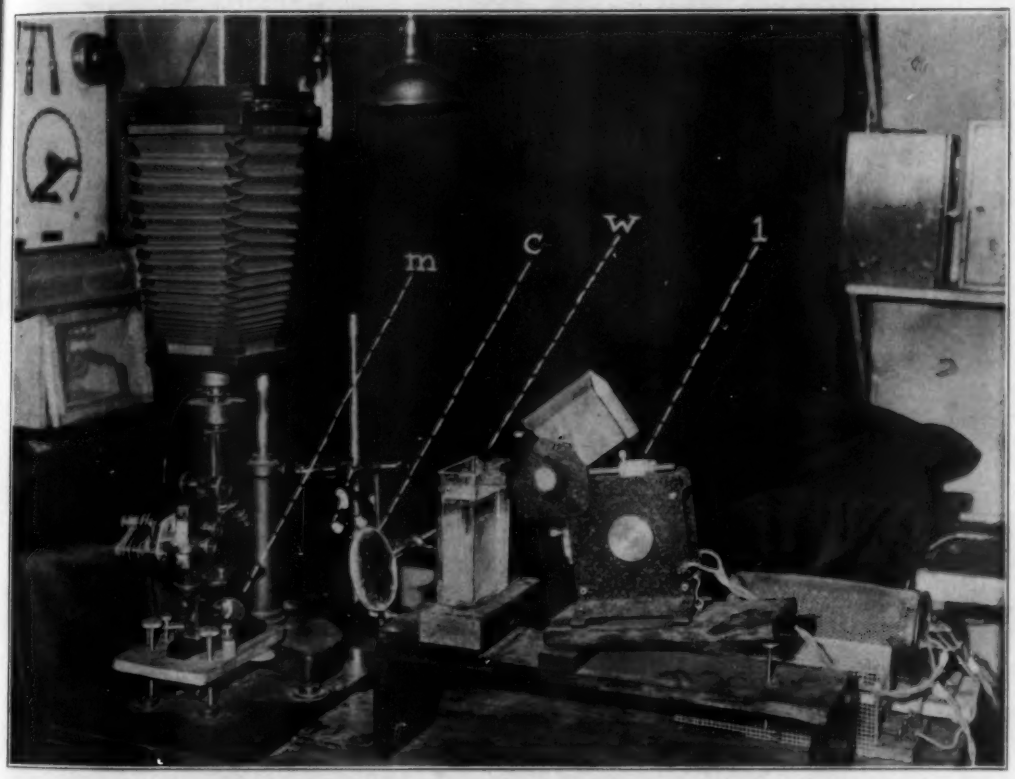

Fig. 1.—Ensemble of apparatus for photomicrography of the blood platelets; arc lamp, *1;* water cell, *w;* condensing lens, *c;* mirror, *m.*

Specimens of oxalated and citrated blood were centrifuged, and the uppermost layer of cells, consisting largely of platelets and white cells, was then pipetted off and used for microscopic observations. While the platelets kept in plasma appear to remain unchanged for several hours, most of our observations were made immediately after centrifuging.

Under the ultramicroscope, normal platelets appear as silver gray disks possessing a fine granular structure. The platelets are usually well

separated and are seen as a collection of single disks. However, occasionally a few platelets appear to be slightly agglutinated. Rarely a platelet is found which has a small protuberance, presenting the appearance of a projecting horn or tail.

Recent investigations have demonstrated the importance of the platelets in cases of thrombocytopenic purpura. In this connection the following cases have been studied.

REPORT OF CASES

CASE 1.—In this case of a chronic intermittent type of hemorrhagic purpura splenectomy had been performed. The case has been reported in detail by Giffin.[2] The initial observations were made two days after splenectomy. The platelets exhibited marked morphologic changes. These changes were of two general types: first, considerable irregularity of variation in shape and size in many instances with protuberances on the platelets, sometimes two or three to each platelet, resembling horns or tails; and second, changes in the appearance of the granules.

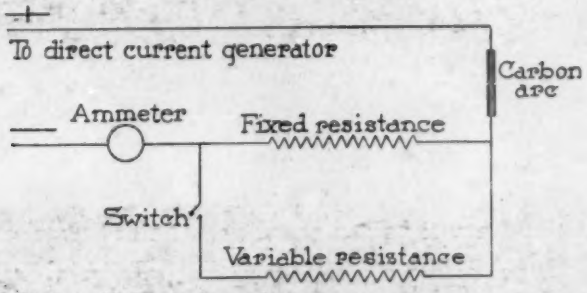

Fig. 2.—Diagrammatic sketch of electrical circuit; ammeter; fixed resistance; variable resistance to throw in parallel with the fixed resistance; switch, and carbon arc.

In the normal platelets, the granules were uniformly a silver gray. Many platelets exhibited much coarser granules, which, in turn, had a much higher brilliance or luster. Samples of blood were examined several months after splenectomy (June 6, 1925), and the platelets were found to be almost normal. A few had protuberances, but if the history of the patient had not been known, the platelets would have been classified as normal (fig. 3).

CASE 2.—Observations were made in this case before splenectomy. The platelet count fluctuated between 80,000 and 100,000. Clinically the purpura was not of severe type, and at operation later atrophic cirrhosis of the liver was found. The purpura may have been entirely a secondary manifestation in spite of the fact that its features both from the clinical and the laboratory standpoints were those of thrombocytopenic purpura. A study of the blood platelets in this case showed the same characteristics as in Case 1, but less marked. The photomicrographic results are reproduced in figure 4.

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2. Giffin, H. Z.: Four Cases of Hemorrhagic Purpura with Splenectomy, M. Clin. N. Amer. **8**:1153-1161, 1925.

Fig. 3.—Normal platelets after splenectomy; × 1900. Reduced approximately one-half.

Fig. 4.—Plates in thrombocytopenic purpura; × 1900. Reduced approximately one-half.

CASE 3.—In a case of pernicious anemia in the late stages hemorrhagic features had appeared. The coagulation tests were similar to those in cases of hemorrhagic purpura, and the platelet count was low, varying from 58,000 to 114,000. A study of the blood showed platelets that were morphologically normal. There were no alterations in the platelets in a number of cases of pernicious anemia which were studied.

These findings suggest the value of a careful morphologic study of the platelets in cases of purpura and diseases that simulate it in certain features. The extreme brilliancy of the platelets under the ultramicroscopic methods of examination, which far exceeds that of any method of staining, adds weight to the suggestion that ultramicroscopic methods be employed in counting platelets. The ordinary form of counting chamber is too thick to be of use. It is possible to attach a ruling to the chamber used with the Siedentopf condenser and to substitute a glass for the quartz condenser. The ordinary dark-field illuminator might also be substituted for the more expensive cardioid condenser.

SUMMARY

We have described or discussed in this paper: (1) simple and inexpensive pieces of apparatus and their ensemble, whereby photomicrographs of the blood platelets may be obtained with periods of exposure varying from one-half to one-fifth second, under a magnification of about 1,900; (2) the morphologic changes in the blood platelets, both immediately prior to and immediately after splenectomy, and the return of the platelets to a normal condition some months after splenectomy in a case of hemorrhagic purpura; and (3) the value of careful morphologic studies of the platelets in cases of purpura, and those that require differentiation from it.

THE SIGNIFICANCE OF VARIATIONS OF BILIRUBINEMIA *

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Recent medical literature contains numerous reports on studies of bilirubinemia. New interest in the subject has undoubtedly been awakened by the introduction of adequate methods for the quantitative estimation of bilirubin in the blood serum. Many of the reports are from the clinical departments of the hospitals, where investigations have been made possible because of the simplicity of the new tests. For the most part, determinations of the bilirubin content of the blood have been made in studies of liver function. Since bilirubin is an excretory product of the liver (perhaps also a secretory one), the amount of bilirubin present in the blood ultimately depends on the function of the liver. On the other hand, when consideration is taken of the fact that bilirubin, like urea and sugar, is a normal constituent of the blood, it is reasonable to suppose that its presence there entails relationships in the body beside those that exist between it and the liver. In studying the behavior of bilirubin in various conditions of disease, not only may information concerning the rôle of this substance be disclosed, but it is possible that light may be thrown on certain disorders of the body.

Determinations of the bilirubin content of the blood were made in 485 unselected cases in the New York Hospital. It was seen that in some diseases there exists a normal bilirubinemia, in others a hyperbilirubinemia, while in one condition of disease a hypobilirubinemia was found. These conditions occurred with a striking consistency. In a report [1] of these cases it was shown that the estimation of the bilirubin content of the blood is of definite diagnostic and prognostic help in a number of diseases. For example, in my experience no case of pneumonia with a normal bilirubinemia ended fatally. Although death did not occur in all cases showing a hyperbilirubinemia, no fatal cases occurred without this condition. In many of the cases it was not possible to foretell the outcome of the disease from the clinical aspect. Further observations perhaps will be of wider interest, for it is possible that a classification of pneumonia based on the bilirubin content of the blood may offer a means of determining a choice of therapeutic measures.

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1. Bernheim, Alice R.: The Icterus Index (a Quantitative Estimation of Bilirubinemia), J. A. M. A. **82**:291-295 (Jan. 26) 1924.

In gastric ulcer there is a normal bilirubinemia, while in duodenal ulcer (except in cases with hemorrhage) there is a hyperbilirubinemia. It may be supposed that an extending duodenitis or adhesions about the gallbladder may account for the abnormal bilirubin findings. Cases of clinical jaundice accompanying duodenal ulcer have been described in the literature. On the other hand, in a number of cases of duodenal ulcer a red blood cell count higher than normal has been found. This may account for the increase in serum bilirubin. With an increased number of red cells in the blood, in all likelihood a greater number undergo destruction, thus producing more hemoglobin for the formation of bilirubin. The finding of a hyperbilirubinemia in two cases of polycythemia vera supports this assumption. Further bilirubin and red blood cell (hematocritic) estimations may possibly disclose a basis for differentiating two types of duodenal ulcer.

A previous report contains the findings in other diseases. Among these the disclosure of the existence of a hypobilirubinemia is worthy of further mention; for this condition not only denotes a secondary anemia, but offers, in addition, supporting evidence concerning the source of bilirubin.

SOURCE OF BILIRUBIN

Recently Rich,[2] in an excellent presentation of the subject, has considered the evidence as to the source of this substance. He concludes that there is no convincing proof that bilirubin has any source other than hemoglobin. He summarizes the data as follows:

1. Hematin and bilirubin are closely related chemically.

2. Hemoglobin spilled into the tissues almost anywhere in the body may be transformed, locally, into bile pigment.

3. The presence of an excess of hemoglobin in the circulation, whether introduced in pure form experimentally or liberated during hemolysis in pathologic conditions, is regularly followed by an increased formation of bile pigment.

To this evidence the existence of hypobilirubinemia may be added as a fourth point. In our series this condition was found in thirty-three cases of severe secondary anemia due to loss of blood from the body by hemorrhage or to disease of the hematopoietic system. In no normal persons was a diminished amount of bilirubin in the blood demonstrated, nor was this found in any other condition of disease.

That this finding is evidence that hemoglobin is a source of bilirubin appears from the following explanation:

Within the body there goes on as a normal process a constant destruction of effete red blood cells. Through this procedure hemo-

2. Rich, Arnold Rice: The Formation of Bile Pigment, Physiol. Rev. **5**:182-219 (April) 1925.

globin is liberated, and the iron-free portion of it is converted into bilirubin. If there is undue destruction of red blood cells, as in pernicious anemia, there is an increased amount of freed hemoglobin, with a resulting increased amount of bilirubin in the serum and in the bile. Where, however, there is no increased destruction of red blood cells but a reduction in their number through diminished production, or through loss from the body by hemorrhage, as in secondary anemia, naturally less hemoglobin is liberated; therefore less bilirubin is formed, with a resulting hypobilirubinemia. In recovery from a secondary anemia when the red blood cell count rises, the bilirubin content of the blood rises proportionately.

A search of the literature has revealed no other report of the existence of hypobilirubinemia. Statements are found to the effect that the serum in secondary anemia is normal, in contrast to the hyperbilirubinemia of the so-called primary anemias. In this series every case of secondary anemia uncomplicated by liver involvement with a red blood cell count below 3,000,000 showed a hypobilirubinemia. That this definite condition has not hitherto been noted is due either to using methods not sufficiently delicate to detect bilirubin values lower than normal, or to rating the normal values too low. Stettin [3] in his report includes hypobilirubinemia within the normal range.

The modified Meulengracht test was used in all cases of this series, the van den Berg test in a large number. The former is more delicate and is found to be more satisfactory for general use than the latter. The modified Meulengracht test measures the depth of color of the serum which is expressed by a number called the icterus index, a term first used by Stettin.

15..... zone of latent jaundice

6.....

normal zone

4.....

2.3..... zone of hypobilirubinemia

The normal icterus index ranges from 4 to 6. Indexes below normal range as low as 2.3. The zone of latent jaundice may be said to lie between 6 and 15 because no case with an index of 15 or below showed clinical jaundice, except those cases in which a preexisting, deeper jaundice was diminishing. Yellow skin and sclerae may persist for some days after the icterus index goes below 15, because bilirubin disappears more rapidly from the blood than from the other tissues. Frank clinical jaundice was evident in all cases showing an index

3. Stettin, DeWitt: The Surgical Value of the Estimation of the Bile Pigmentation (Icterus Index) of the Blood Serum, Ann. Surg. **76:** 191 (Aug.) 1922.

above 15. Thus we find with respect to the degree of bilirubinemia that there are four zones: (1) the zone of hypobilirubinemia, (2) the normal zone, (3) the zone of latent jaundice, (4) the zone of frank jaundice.

It is unfortunate that some investigators who have surveyed the tests for hepatic function have discarded the Meulengracht test because of its possible sources of error; for these errors are easily controlled, and the test is simple, delicate and reliable.[4] Objections are offered to the test because: (1) The color of the serum may be due to pigments other than bilirubin. (2) The serum may be cloudy. (3) The serum may be hemoglobin stained, and as a result false readings may be obtained.

In reference to the first objection, it is true that the yellow color of the serum may be deepened after the ingestion of carotin and xanthophyll, pigments that occur in animal and vegetable substances, such as eggs, oranges, carrots, etc., thus producing what Hess and Myers have described as a carotinemia. In order to determine whether this condition is a controllable factor, the following experiment was made: a carotinemia was brought about in four normal persons by feeding them a meal of carrots. Three of the subjects of the test ate the same amount of carrots, while the fourth ate double the amount. The icterus indexes were 5, 5, 5 and 6 before the meal. Three hours later they were 9, 9, 8 and in the one who ate the double portion of carrots, 15. The following morning the figures were again normal. In a number of other experiments with diabetic persons and others it was shown that in the case of a high icterus index due to carotinemia, the serum after a twelve hour fast is free from any appreciable amount of coloring matter other than bilirubin. Hence, if the blood be taken for icterus index estimation before breakfast after a night's fast, it is possible not only to rule out carotinemia but to avoid any cloudiness due to digestion. Greene, Snell and Walters [5] cite two cases of patients with pronounced discoloration of the skin and carotinemia after the prolonged use of carrots in their diet. The icterus index in one case was found to be 18, but, as determined by chemical methods, the serum bilirubin measured only 0.5 mg. per cent, an entirely normal amount. In the second case the icterus index was 26, but the serum bilirubin was only 1.1 mg. per cent. The existence of this condition is considered a contraindication for the use of the Meulengracht test. Even if chemical

4. The technic of the modified Meulengracht test has been described in a previous report. Since then the technic has been simplified and a source of error removed by the substitution of a glass standard for the 1:10,000 potassium dichromate solution. This new standard may be obtained from Eimer and Amend, New York City.

5. Greene, Snell and Walters: Diseases of the Liver. 1. A Survey of Tests for Hepatic Function, Arch. Int. Med. **36**:248-272 (Aug.) 1925.

methods are necessary in these cases (since it is conceivable that a carotinemia of such intensity may disappear less rapidly than that produced after ordinary meals), this is no indication against the general use of the Meulengracht test, because such intense carotinemia is rare, and the nature of the pigmentation can be disclosed with the aid of the dietary history.

With carotinemia and cloudiness of the serum under control, hemolysis remains as the only other objection to the Meulengracht test. To obtain serum unstained by hemolysis is generally a matter of careful technic. Dry needles and tubes are necessary, and to prevent the hemolyzing effect of the water of condensation which may form when warm blood is let into a cold container, as Dr. A. F. Coca has shown, the blood may be rapidly cooled by letting cold water run over the syringe immediately after the blood has been drawn.

Some investigators prefer the van den Bergh test for the estimation of bilirubinemia. With this test, however, it is not possible to measure the zone of hypobilirubinemia, nor can the zone of latent jaundice be so accurately defined with it as with the modified Meulengracht test, possibly because of the loss of some bilirubin, which occurs in performing the test.

THE ICTERUS INDEX

The consistency with which the icterus index has been found to occur within a definite zone as a characteristic finding in various diseases in over 4,000 cases examined, not only speaks well for the accuracy of the modified Meulengracht test, but also provides a basis for a comparative study of the constituents of the blood. For example, the comparison of the icterus index and blood sugar findings in the normal person with those of the diabetic person reveals an interesting relationship.

In the diabetic person the icterus index is found to be high. Of the forty-one patients examined in the New York Hospital, none showed a normal index. The lowest index was 7.5, the highest 15, while the average figure was 10. The deep yellow color of the serum in this disease has been observed by a number of investigators, and has been attributed to a carotinemia due to the large amount of vegetables eaten by diabetic persons. There is convincing evidence, however, that the depth of color of the serum is due not to a carotinemia but to a hyperbilirubinemia:

1. The severe cases of the disease showed the highest indexes.

2. In eight of these cases the icterus index was determined on the last day of a three-day milk diet, thus ruling out the influence of pigment-bearing foods.

3. In six of these cases there had been no previous diabetic diet.

4. The indirect van den Bergh test performed in seven cases, all showing icterus indexes above normal, showed a hyperbilirubinemia in five cases. (It is possible that the normal figures in the two cases may be due to some loss of bilirubin, the aforementioned fallacy of the test.)

What is the cause of the hyperbilirubinemia in diabetes? In an effort to determine whether there is any relationship between the high icterus index and the high blood sugar of this disease—possibly a common cause for both—it was thought that estimations of bilirubin and sugar under controlled conditions might be of interest. Accordingly, these were made during glucose tolerance tests performed on seven normal persons and on seven diabetic persons. The first determinations were made before the ingestion of the glucose (1.5 Gm. per kilogram of body weight). Subsequent ones were made one-half hour, one hour, one and one-half hours and two hours after its administration.

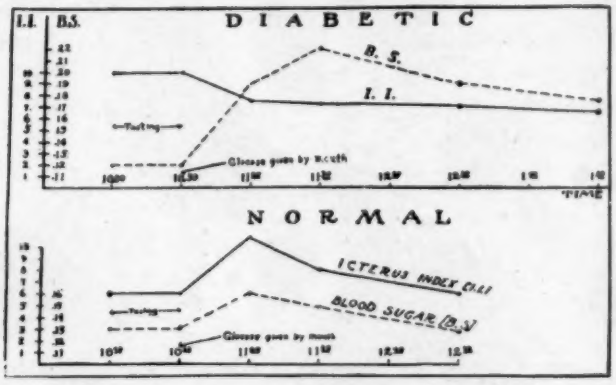


Chart 1.—Blood and icterus index findings in normal persons and in diabetic patients.

For the sake of clearness only one case of each group is shown in the chart. All cases showed curves characteristic of their group. In these two sets of cases a definite difference was seen in the behavior of the bilirubin in relation to the sugar. In the normal person the icterus index was seen to go up with the rise in blood sugar, whereas in the diabetic person the icterus index went down when the blood sugar rose.

Attempts to explain these phenomena are based to some extent on conjecture. Summing up our knowledge concerning bilirubin, we find that we know one of its sources (probably it is the only one), that it occurs as a normal constituent of the blood and bile, and that under certain conditions its character and amount are altered. We have no definite knowledge of where it is produced. There is, however, convincing evidence that it is not formed by the polygonal cells of the liver.

MacNee's new theory of jaundice, which has found widespread support, is based on the results of animal experiments presenting suggestive evidence that bilirubin is formed by the cells of the reticuloendothelial system. The rôle of the polygonal cells in regard to bilirubin is mainly an excretory one. They remove bilirubin from the blood and excrete it into the bile. In its passage through the polygonal cells, however, it undergoes some change, as is indicated by the van den Bergh test. The bilirubin in the bile gives the immediate direct reaction, whereas the bilirubin normally present in the blood, which has not passed through the polygonal cells, gives the delayed direct or the indirect reaction only.

SIGNIFICANCE OF BILIRUBIN CONTENT OF BLOOD

In the light of our present knowledge and opinions, interpretations of the significance of the bilirubin content of the blood depend on the following factors: (1) the number of red blood cells destroyed—producing the supply of hemoglobin; (2) the condition of the reticuloendothelial system—converting hemoglobin into bilirubin; (3) the function of the polygonal cells of the liver—taking bilirubin from the blood and conveying it to the bile; (4) the character of the bile—affecting its passage through the bile canaliculi; (5) the patency of the bile ducts.

With these considerations in mind the findings in the glucose tolerance tests in normal persons would seem to depend on the function of the polygonal cells of the liver. The rise in the icterus index at the half-hour periods in the tests mentioned above may accordingly be explained in the following manner: at the end of one-half hour the polygonal cell of the liver may be said to be engaged in storing the ingested sugar. Nothing in our knowledge of the permeability and reactivity of cells has yielded evidence to indicate that a cell if presented with an increased amount of a substance for which it has a selective action is rendered unable to remove from the blood other such substances present in normal amounts. It is conceivable, however, even though not indicated by the present data of cell chemistry, that while the liver cell is storing the large quantity of sugar it is not able to take up bilirubin, and the temporary accumulation of bilirubin in the blood accounts for the high icterus index at this period.

In diabetes evidence points to disturbance of the liver. We know that, because of the lack of insulin, the polygonal cell cannot store its glycogen. We do not know in what way the liver cell is affected to produce this disorder. The fact that normal function is regained even in long standing cases on the administration of insulin speaks against actual damage to the cell by the lack of this substance. A better understanding of the question will be obtained, however, only when the

fundamental chemicophysical reactions of cell metabolism are known. In our present state of knowledge we are able to consider only the results of these reactions as witnessed in the changed activity of the cell.

In considering the altered activity of a disordered cell three possibilities present themselves: (1) an over-activity, (2) an under-activity, and (3) an activity altered in character. How may the increased blood sugar in the diabetic be accounted for in terms of liver cell activity? A normal liver cell in respect to sugar is active (1) in removing sugar from the blood, (2) in converting it into glycogen, (3) in storing the glycogen, (4) in reconverting the glycogen into sugar in response to the body's need for it.

Failure of the diabetic liver cell to store the normal amount of glycogen may conceivably be due to its inability to remove normal amounts of sugar from the blood, and this would account for the high blood sugar as well as for the diminished store of glycogen. In other words, the cell may be underactive (less permeable?); on the other hand, sugar may be taken up from the blood at a normal rate, but the processes of converting it into glycogen and storing the glycogen may be affected so that the sugar will straightway enter the blood again. The third possibility is that sugar may be taken up, converted into glycogen and returned to the blood with greater than normal speed (increased permeability?); that is to say, the diabetic cell may be an overacting one in regard to sugar.

If the liver cell in diabetes is an overactive one, the high icterus index in this disease may be explained in the same manner as in the case of the normal person during a glucose tolerance test: the liver being overactively engaged in removing the increased amount of sugar from the blood cannot perform its function of removing bilirubin at the normal rate of speed. Thus the usual condition of the liver cell in diabetes is like that of the normal cell when stimulated into overactivity in removing an increased amount of sugar from the blood.

During the sugar tolerance test in the diabetic patient, there was a fall in the icterus index with the rise in blood sugar. Attempts to explain this phenomenon lead us more deeply into the realms of speculation. Possibly the already overburdened liver cell when presented with a sudden increase of sugar is overwhelmed and thrown into inertia with respect to removal of sugar, and can at such a time remove more than the usual quantity of bilirubin.

That the liver cell in diabetes is overactive in regard to another substance is shown in the liver function test with phenoltetrachlorphthalein. In five of the six diabetic patients in whom this test was performed, the dye disappeared more rapidly from the blood than in any normal subject. In the five cases only from 2 to 3 per cent of the dye remained in the blood fifteen minutes after injection. One case

showed a 5 per cent retention. At the end of an hour no dye was found. The test performed on ten normal persons showed not less than 5 per cent at the fifteen minute period, and in six of these cases there was a trace of dye in the blood an hour after injection.

Icterus index determinations made simultaneously with the phenol-tetrachlorphthalein tests showed an increase in bilirubin at the hour

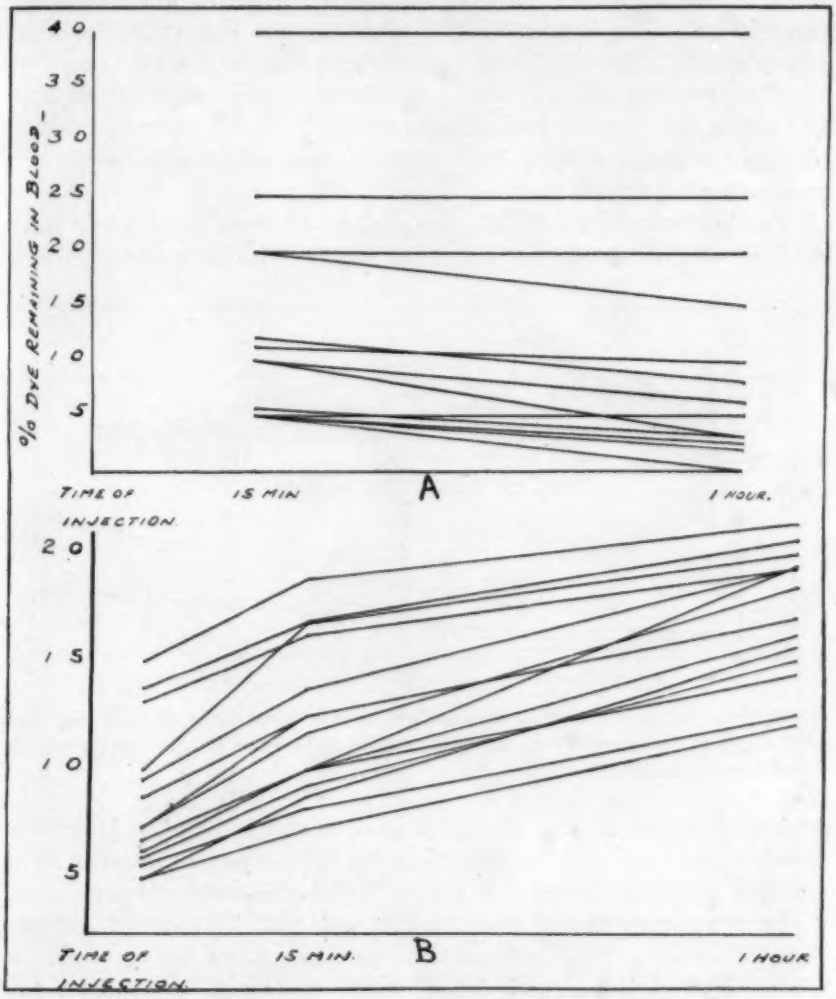


Chart 2.—*A*, liver function test; *B*, icterus index in twenty-one varied cases.

but none at the fifteen minute period. On the other hand, the same estimations made in twenty-one varied cases (nondiabetic) during a liver function test showed a distinct rise in the icterus index at the fifteen minute period and a still further rise at the end of an hour.

The rise in icterus index which occurred at the end of an hour in both series may be the consequence of the toxic action of phenol-

tetrachlorphthalein on the liver, and, until it has recovered, the liver cell cannot properly perform its function of removing bilirubin from the blood. In slightly greater concentrations than that used for the liver function test the toxic effects of this dye are marked, and in experimental animals necrosis of the liver has followed its injection.

Interpretations of the rise in icterus index at the fifteen minute period in the nondiabetic cases may be made in terms of the aforementioned suppositions. The liver cell while removing the dye from the blood cannot at the same time remove bilirubin. In the diabetic cases the already overacting cell may not be stimulated to greater activity in order to remove the dye (it may be as permeable to the phenoltetrachlorphthalein molecule as to that of glucose), hence the status of bilirubin removal remains unchanged.

Further estimations of bilirubin and blood sugar were made while the liver was being stimulated in other ways. The determinations were

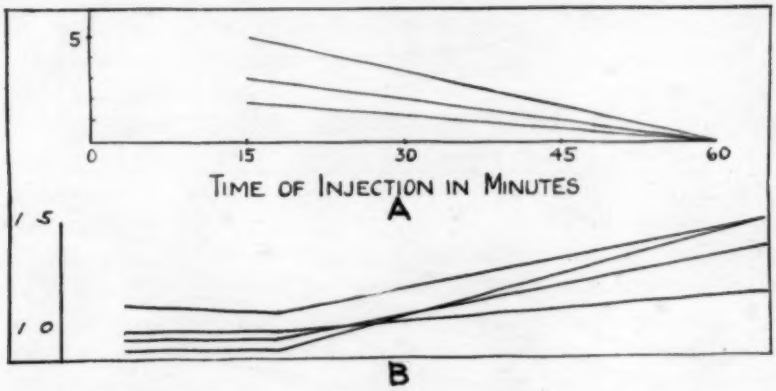
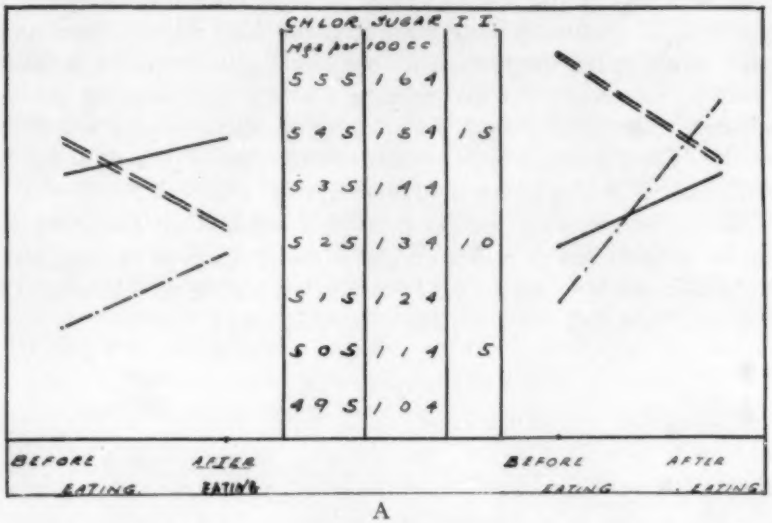


Chart 3.—*A*, liver function tests and, *B*, icterus index estimations in six cases of diabetes. The numbers at the left side in *A* indicate the percentage of dye remaining in the blood.

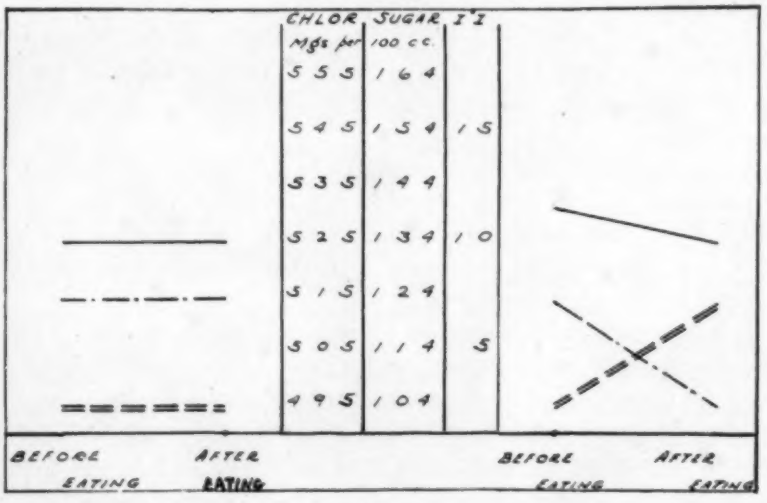
made first in the fasting state and were then made immediately after eating before food could be absorbed from the stomach or intestine, after smelling food while hungry, and after the administration of cinchophen.

In four cases blood urea nitrogen and chloride estimations were likewise made. The subjects of the test were normal persons whose icterus index and blood sugar had been determined and shown to be normal on several occasions. One person had repeatedly shown a high icterus index of unknown origin (perhaps a case of van den Bergh's physiologic hyperbilirubinemia). On the occasion of this test in the fasting state the icterus index and the blood sugar values were found to be higher than normal in all cases. After eating in the first two cases, there was an identical rise in the icterus index and in

the blood sugar—36 per cent in case 1 and 10 per cent in case 2. The urea nitrogen did not change, but the chlorides went down after the meal. In case 3 there was no appreciable change after eating in any of the estimations. The subject in this case likewise failed to react in other



A



B

Chart 4.—*A*, chlorides and sugar in cases 1 and 2 before and after eating; *B*, estimations of icterus index, blood sugar and blood chlorides in normal cases 3 and 4 before and after eating. The unbroken line indicates the icterus index; the dash and dot line, the blood sugar; the parallel dash line, chlorides.

similar experiments in which other persons have shown changes in the icterus index and blood sugar figures. In case 4, that of the person who repeatedly showed a high icterus index, both the index and the blood sugar went down after eating, while the chlorides increased.

An element of unexpected interest appeared in these four cases in the explanation of the high figures found in the fasting state. Now and then for a week or two before the experiment, an odor of illuminating gas had been noticed in the laboratory where the four people worked. A test of the jets, however, revealed no leakage of gas. On Dr. Ralph G. Stillman's suggestion that the high icterus index might be due to an undue destruction of red blood cells from the inhalation of carbon monoxide, a more thorough search for escaping gas was instituted. This time a small leak from a hidden gas pipe was found. Two days after the pipe was repaired estimations of icterus index and blood sugar showed a return to normal figures.

Further experiments are being carried out in this laboratory with cases of diabetes before and after the administration of insulin, and in other conditions in which a high icterus index occurs, such as exophthalmic goiter, duodenal ulcer, pernicious anemia, etc.

COMMENT AND SUMMARY

Observations of the variations in bilirubinemia are chiefly directed to the study of liver function, but bilirubin, besides being a product of the liver, is a normal constituent of the blood, and as such plays a rôle of some importance in a number of conditions not primarily concerned with the liver.

The accuracy of the test for the determination of the icterus index and the facility with which it is performed make it available not only for investigations in hospitals, but also for the use of the outside practitioner.

As a diagnostic and prognostic aid in a number of diseases, the determination of the icterus index is a procedure which may be said to hold equal rank with other laboratory tests, such as those for blood sugar, urea nitrogen and creatinine, with an advantage over these tests in that it is simpler to perform.

It is seen that under controlled conditions in which the liver is stimulated, blood sugar and bilirubin values bear a definite relation to each other. Explanations of these findings are presented with due recognition of the conjectural element involved, and with the hope that further evidence may either substantiate them or show why they are incorrect.

OPPORTUNITIES FOR CLINICIAN AND PATHOLOGIST OFFERED BY THE STUDY OF HUMAN CONSTITUTION

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One of the oldest and soundest ideas which recurs throughout the history of medicine is that disease results from the disastrous interaction between man and his environment. Thus a triad of problems is ever presented to the investigator—the individual, the disease process expressed in clinical and structural change and the special injurious agent of environment. At various epochs some one of these three aspects of medicine has enlisted greater attention from the profession than the others. The intensity and duration of investigative work on any one of the three has depended largely on the adequacy of such technical methods as existed or could be devised. Notwithstanding the emphasis which the fashion of medical thought of the moment has put on one or another phase, every well trained physician has sought to gain some knowledge of them all. At the outset, when known facts were comparatively few, this task lay within the scope of one man's capacity; but as the mass of information expanded beyond this point specialization in fields of research, as well as therapeutics, naturally developed. The older admonition and example of Hippocrates and Galen to study the natural history of man from the book of life, was succeeded by the investigation of disease as expressed in the morbid process. Then just at the time when the great British clinicians of the late seventeenth and early eighteenth centuries were reviving interest in the individual or constitutional factor, Pasteur opened the door to the exact study of the adverse forces of environment. Thereafter, for a time, medical thought and investigation turned energetically in their direction. Consideration of the individual as a causative factor in his own ailment was almost forgotten; and pathology, following the lift given by the freshening impulse of Virchow, was carried on as an accepted hospital routine. Many pathologists, with clinicians, bacteriologists and pharmacologists, became investigators of the injurious effects of environment on animal organisms. But there has been one chapter in the book of pathology which has always received great attention and constant additions. There is no more fascinating or better recorded set of observations in medicine than those dealing, not with disease process, but with structural anomalies. These variations in form, of either an organ, a skeletal part, or the whole individual, have unconsciously pinned the attention of pathologists on the potential variability

of the human organism. Indeed, the point at which a structural variation becomes pathologic is as often a matter of degree as of kind. Thus, for example, a perfectly functioning lobulated kidney arrests the attention at necropsy quite as sharply as does the swollen or contracted and granular organ of nephritis. Moreover, very large or very small persons, who are accepted as normal variants of the racial type, are but a step removed from pathologic giants or dwarfs. Consequently, there is always passing under the eye of the pathologist material which must draw his thought toward the background which the individual himself supplies and which is essential to the pathologic process. In this respect the pathologist shares with the clinician continual opportunity to study and reflect on the nature of man. Many of the phenomena which appear to either group of observers express modifications of the growth and development processes. The mechanism by which certain growth faults arise has been ably demonstrated by Stockard,[1] Newman[2] and others. The former showed that various types of double monsters could be produced by retarding the rate of development of the fertilized egg. As a result of his extensive studies, he concluded that all types of monsters (not hereditary) are the result of developmental arrests. Newman was able to produce certain types of monsters by hybridization. Obviously, then, structural anomalies of all sorts, whether sufficiently gross to be termed pathologic or not, provide important material for the student of human growth and development. At once the door is opened to a study of heredity as well as to the effects of environment on the immature individual.

The clinician likewise in such conditions as giant hand or finger (localized overgrowth), acromegaly, gigantism, dwarfism, adiposity, incomplete twining, and many others, may observe phenomena which throw light on the growth and development processes of what, for want of a more accurate term, may be called the normal specimen. The foregoing conditions are well discussed by Hastings Gilford.[3] Obviously, growth and development, determined as they are by the joint action of heredity and environment, produce the finished specimen. The success or failure which such a product, called the phenotype, achieves in adapting itself to environment expresses the quality of its constitution. There have been many criteria described by which the capacity of a given person's constitution might be judged. Thus,

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1. Stockard, C. R.: Development Rate and Structural Expression, Am. J. Anat. **28**:115, 1921.

2. Newman, H. H.: On the Production of Monsters by Hybridization, Biol. Bull. **32**:306, 1917.

3. Gilford, Hastings: The Disorders of Postnatal Growth and Development, London, 1911; Relations of Biology to Pathology, Brit. M. J. **1**:1279, 1912.

Hippocrates pointed out that people who lived in moist countries were fat, hairless, like women, and resisted disease poorly; whereas those who lived in colder, rockier regions were sleek and wiry and hardy. Laymen have noted the importance of good color and eye light as indications of health. But observations of this kind deal entirely with the exterior of the body, its contours and proportions. Beneke [4] was among the first to point out important structural anomalies in the arterial system. In 1798, he showed the association of the small aorta with an inadequate constitution, stating that persons possessed of such an arrested arterial development rarely survived long. In 1632, Spigeluis [5] described a ratio between intestinal or body length. Later, Treves [6] drew attention to the difference between the intestinal lengths of carnivorous and herbivorous animals. He showed that in the former the intestine was short, and in the latter long and tortuous. These differences could be traced in sharply defined parallel through successive species down to the lowest orders. Treves believed that intestinal length thus provided a dependable means, not only for classifying species, but also for demonstrating phylogenetic relationship. This work was followed up by Bean,[7] who correlated with intestinal length numerous observations on body form and disease propensity. These correlations formed the basis of his classifications of mankind. In 1915, Bryant,[8] also working on the difference in intestinal lengths, offered a classification of human beings on a morphologic basis, and pointed out somewhat similar disease correlations to those of Bean.

DISEASE GROUPS OR RACES

The studies at the Constitution Clinic of the Presbyterian Hospital in New York have been undertaken from a rather different angle. Their purpose has been the same as that pursued by medical observers since the earliest times; namely, the investigation of the individual. The plan of this study hinges on the classification of mankind according to its disease potentiality. It has been assumed that if one is justified in classifying disease according to the environmental agent which produces it, to classify it in respect of the subject's ability to develop it is equally logical; for surely a subject is as necessary to the production

4. Beneke, F. W.: Alterdisposition, Marburg, 1879; Ueber das Volumen des Herzens Schriften. d. Gessellsch. Nat. Marburg. suppl. **2**, 1879.

5. Spigelius: De Humani Corporis Fabrica, Lich. VIII, cap. IX, Frankfurt, 1632, 293.

6. Treves, Sir. F.: Brit. M. J. **1**:583, 1886.

7. Bean, R. B.: Morbidity and Morphology, Bull. Johns Hopkins **23**:363, 1912.

8. Bryant, John: The Carnivorous and Herbivorous Types in Man, Boston M. & S. J. **172**:321, 1915.

of pneumonia as the pneumococcus. Seven disease groups or races were chosen; namely, gastric ulcer, gallstone disease, asthma due to protein sensitization, acute rheumatic fever, pernicious anemia, hypertension and nephritis, and diabetes. All members of each of these disease races have been subjected to certain special forms of study which are discussed in detail in my book.[9] Therein is described the plan of making coordinate studies of the individual's anatomic, physiologic, psychic and immunologic characters. For the investigation of the anatomic or morphologic character, recourse was made to the excellent existing technic of physical anthropometry. In 1864, di Giovanni [10] of Padua had made extensive studies of morphology by mensuration, but had implied that disease developed in an individual because of his anatomic structure. This position has seemed to us to be unjustified. Rather does it appear more logical to look on morphology, function, psychic pattern and immunity character as coordinate values within the phenotype, and thus expressive of the environmentally modified genetic plan. Up to the present time, the only published reports of our work have dealt with the morphologic character. Now, notwithstanding the extent of variation which one would expect to find in so completely hybridized a species as man, and likewise notwithstanding the fact that throughout nature there is no absolutism, nevertheless these studies of disease groups have disclosed differences in type sufficiently striking to justify comment and further investigation. The number of cases, averaging between ten to forty in each disease group, is obviously small; yet the method of analysis apparently has been adequate to display not only the absolute differences, but also the frequency and degree of overlapping of types. To illustrate the distribution of cases, for example, in respect of the gonial angle character in the gallbladder race versus the gastric ulcer race, the following figures are quoted:

Of seventeen male patients with gallstone disease, six showed a gonial angle of less than 110 degrees; eleven between 110 and 120 degrees, and none above this. In the gastric ulcer group of thirty patients, eight were between 110 and 120 degrees; but twenty-two were between 120 and 135 degrees. There was only one case with an angle of less than 115 degrees. So it appears that there is an overlap between these two disease groups in the gonial angle character between 110 and 120 degrees. Approximately 64 per cent of the gallstone group and 20 per cent of the gastric ulcer group fall in this common zone. But 29 per cent of the colilithiasis group, and 73 per cent of the gastric

9. Draper, George: Human Constitution, Philadelphia, W. B. Saunders Company, 1924.

10. Di Giovanni, A.: Clinical Comments. Deduced from the Morphology of the Human Body, Trans., London, 1909.

ulcer race fall completely outside and on opposite extremes of the overlapping zone. In considering this particular disease race, it must be remembered that the rareness of male gallbladder cases is such as to make a large group difficult to collect. Similar studies of the degree of overlapping have been made for a large number of characters and between different disease groups. The foregoing discussion of the gonial angle in the gallstone disease group and gastric ulcer group is given simply as one example. In a more general way, attention may be called to numerous other differences between these two disease races which occur in the upper jaw; for example, even in the upper jaw alone many striking differences are found between the groups. Thus, for instance, the palate of members of the gallstone group is broad and shallow, and the ratio of the anterior breadth (between canines) to posterior breadth (between second molars) is high. This gives a square, U-shaped jaw. The palate of ulcer people, on the other hand, is narrow and deeper, and the ratio just described is lower. This results in a more oval anterior portion of the palate. The teeth likewise show differences, not only of position, but also of size and shape. In the gallstone people the teeth are short and square, with the lateral incisors nearly as wide as the centrals. Vertical or lingual version is the rule. Furthermore, the line of the free margin of the teeth is straight, and the biting edge is broad and dull. Gastric ulcer people, on the other hand, have longer, narrower teeth, and the lateral incisors are often only half as wide as the central incisors. Version is nearly always labial. The free margin forms a waving line, and the biting edge is sharp. The scope of the paper does not permit further discussion of the jaws of the other disease groups; but there are numerous striking and constant differentiating characters to be found in them which will be reported subsequently.

Throughout the rest of the body measurements, which with few exceptions are applied direct to the bony skeleton, show equally striking and constant differences between the disease representatives. Thus, about the face it is found that gallbladder people have broader, shorter faces than do members of the ulcer race, yet the eyes of the former in relation to facial diameter are closer together. The gonial angle (formed by the intersecting borders of horizontal and ascending rami of the mandible) averages 112 degrees in gallbladder people, and 120 degrees or more in the ulcer race. The thorax of the former group is large in all dimensions, whereas in the latter, while chest length is equally great, the anteroposterior diameter is much flatter. An outstanding thoracic feature of the gallbladder race is the wide subcostal angle, which averages 50 degrees or more. Our finding of a narrow angle (average, 40 degrees or less) in the gastric ulcer group explains

the surgeon's complaint that the proximity of the costal margin is always an annoyance during operations for ulcer. If the distance from the base of the xyphoid to the umbilicus be measured and that value used as the denominator of a fraction whose numerator represents the distance from the umbilicus to the upper edge of the symphysis pubis, the resulting ratio will indicate the position of the umbilicus on the abdominal wall. It has been found that gallbladder people have a low figure for this index and ulcer people a high one. Finally, it is found that the breadth of pelvis of gallbladder people is very great. But the most interesting point about this finding is that males of the gallbladder race have a pelvic diameter which, relative to shoulder breadth, is as wide or wider than that of the female. Males of this race also tend to fatness, and their contours suggest feminism. Thus it appears that the ulcer race is, in general, slender and composed chiefly of men. The gallbladder race, on the other hand, is thickset and fat, and composed chiefly of women. But those males who do develop gallstone disease present characters of bony skeleton and soft part development strongly suggestive of feminism. This observation has opened a vista of great interest concerning the influence of the sex factor in determining the constitutional reaction in disease. As a result of these observations, which are fully discussed in another communication,[11] it seems justifiable to state that when an individual of one sex develops a disease more common to the opposite sex, he or she presents evidence of incomplete differentiation toward his or her own sex. Space does not permit a discussion at this time of the other ways in which the sex factor seems to play its part in the determining the constitutional reaction. But the importance of further study of this phase of the subject is great because of the relationship of sex to growth and development. Obviously, until these two remarkable phenomena are finally understood, it will be impossible to appreciate fully the qualities of the phenotype. So far our studies have been carried on in a purely objective manner, and simple correlations of morphology and disease potentiality have been made. No explanations have been attempted on a glandular or any other basis. There is much work of a similar nature to be done on the form and variations of the internal organs in the disease groups. As far back as 1765, de Haen[12] discussed the variation in position of internal organs in relation to disease. Later, in a limited study of this character, Nacke[13] showed that in a series of cases of general paresis,

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11. Draper, George: Influence of Sex upon the Constitutional Factor in Disease, New York State J. Med., Dec. 1, 1925.

12. De Haen: Rationis Medendi Viennal Caustrial, pars X, 1765, Tab. 3, 4; pars XI, 1767, Tab. 1, 2, 6.

13. Nacke, P.: Einege innere somatische Degenerationzeichen, etc., Allg. Ztschr. f. Psychiat. **58**:1309, 1901.

there were greater and more frequent anomalies than were found in a control lot of nonparetic cases. Curiously enough, however, anomalies of the liver were more frequent in the nonparetic group.

In conclusion, it may be said that both to the pathologist and to the clinician are given unusual opportunities to study, not only the pathologic processes and symptoms of disease, but also the subject—Man, himself. By careful collection of anomalies of structure, by separating those due to heredity from those induced by the pressure of environment during some moment or more extended time of the growth and development period, much light can be thrown on the special and peculiar nature of any given phenotype.

Laboratory and Technical Notes

VALUE OF KAHN TEST AS APPLIED TO CONTAMINATED ARACHNOID FLUIDS*

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Kendricks[1] has reported that the Kahn test is more reliable than the complement-fixation test when old and contaminated serums are used. In view of the fact that arachnoid fluids are more susceptible than blood serum to contamination and deterioration, it was thought that a study of spinal fluids along the same lines would be valuable.

To establish the effect of age and contamination on the Kahn test, arachnoid fluids that had been tested by the complement-fixation test immediately after drawing, were allowed to remain in the icebox for a period of one month, and then were tested by the Kahn test. No effort was made to prevent contamination, and all of the fluids became contaminated.

Fifty fluids were taken and treated as indicated. In only one instance did the complement-fixation and the Kahn test fail to agree. There were thirty-nine fluids that gave negative tests by both methods, and ten fluids that gave positive tests by both methods. One fluid gave a positive complement-fixation test and a negative Kahn test.

The only necessary departure from the technic as described by Kahn is that the fluids were centrifuged at high speed for ten minutes before being treated with ammonium sulphate solution, to clear them from bacterial growth as completely as possible. Practically all of the fluids remained cloudy after this centrifuging, but there were no visible particles. This cloud of bacteria did not seem to interfere with the precipitation and the reading of the results.

The high degree of accuracy of the Kahn test under such adverse circumstances is surprising. Spinal fluids that are contaminated in any degree are unfit for the complement-fixation test, and even several days age without contamination renders the results of the complement-fixation unreliable or anti-complementary. This is a great aid in that spinal fluids that have to be mailed or held for any unusual period may still be utilized for a reliable diagnostic test.

The complement-fixation test that was used in the comparison was the two tube Kolmer technic. The Kahn test was made exactly as described by Kahn, except for the initial centrifuging.

Of course fifty fluids do not give a reliable number on which to base conclusions, and a larger number would, in all probability, give more variable reactions. The main conclusion to be reached from such a study is that for spinal fluids the Kahn test can still be used with a fair degree of reliability even after the specimen is old and contaminated.

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*From the Laboratory of the Methodist Hospital, Memphis, Tenn.

1. Kendricks, P. L.: Effect of Age and Contamination on Kahn Precipitation Test, Am. J. Pub. Health **14**:673 (Aug.) 1924.

General Review

THE PATHOLOGY OF BURNS*

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A burn is an injury inflicted on the body by a degree of heat higher than is compatible with healthy action in the part affected.

The types of thermal trauma are two: burns are produced by dry heat, scalds by moist heat. The skin is the most common seat of caloric injuries, which are termed dermatitis calorica, of which there are two divisions: dermatitis ambustionis (burn) and dermatitis congelationis (frostbite).

A burn can be caused by any body which radiates much heat. This is commonly due to proximity to, or direct contact with, flame or heated solid bodies, superheated air, gas explosions, inflammable liquids, such as benzine and turpentine; scalds by the action of boiling water, or other liquids, superheated steam and molten metals. The difference in the effects of burns and scalds is comparable to the distinction between roasting and boiling.

The results of burns vary according to: (1) the degree of temperature, (2) the nature of the exciting agent, and (3) its capacity for heat absorption, (4) the duration of contact, (5) the susceptibility of the part acted on, and (6) the condition of the patient.

CLASSIFICATION OF BURNS

The types of thermal trauma may be classified according to whether they are burns or scalds, by the type of the exciting agent—as a gasoline burn, a radium burn—by the area of surface involved and by the depth of tissue invaded or destroyed. The latter is the pathologic classification and the one of choice.

In America and Germany this classification includes three degrees, whereas in France and England, six degrees are used to denote the various depths of skin involvement.

Classification of Dupuytren. (Six degrees.)

1. Erythema of the skin ("phlogose"): Caused by a temperature of 140 F.
2. Vesication: Caused by a temperature of 160 to 210 F.[1]

*From the Department of Pathology, University of Alabama School of Medicine.

1. Macleod, J. M. H.: Burns and Their Treatment, Oxford War Primer, Oxford University Press, London, 1918.

3. Destruction of the cuticle and part of the cutis vera, the tips of the papillary downgrowths remaining intact: Caused by a temperature of 210 F.

4. Destruction of the entire integument and part of the subcutaneous tissue: Caused by a temperature of 210 F. and more, over long exposures.

5. Ecroachment on muscles.

6. Disorganization and charring of the tissue (carbonization).

American Classification.

(*a*) According to Heister and Callison.	(*b*) According to Morton.
(1) Erythema of skin.	(1) Dermatitis ambustionis erythematosa.
(2) Formation of vesicles.	(2) Dermatitis ambustionis vesiculosa et bullosa.
(3) Formation of eschar.	(3) Dermatitis ambustionis escharotica seu gangrenosa.
(4) Charring of the tissue.	

THE LOCAL CHANGES OF BURNS AND SCALDS

In considering the local history, there are three stages to be noted: (1) the stage of destruction or burning, (2) the stage of inflammation and sloughing, (3) the stage of repair.

Degree one begins with a simple erythematous flush. The vascular reactions are similar to those in any inflammation, consisting of a momentary contraction, then a vasodilatation of the arterioles and venioles. This local widening of the capillary bed, due to the direct action of the irritant, is responsible for an increased rapidity of blood flow to the injured part, causing the area to be warmer and redder. Immediately surrounding this injured area is a widely spreading irregular margin, exhibiting a bright arterial flush, which is the result of a local reflex causing a dilatation of the arterioles.[2] While the stream bed remains wide, the current slows and an active congestion of the part ensues. There is a locally increased permeability of the walls of the minute blood vessels, so that a filtering of plasma occurs out into the tissue spaces (inflammatory edema). This superficial skin edema is responsible for the low, flat heat wheals of various sizes that are found. Within the blood vessels, margination of leukocytes occurs with a subsequent migration into the tissue spaces, followed by a diapedesis of the red blood cells. The period of edema ordinarily lasts from thirty-six to forty-eight hours. Within a few days the upper layer of the epidermis separates in the form of scales, or occasionally peels off. Any pigmentation which remains disappears in time. The linear fissures of the skin appear more prominent than usual because of the partial detachment or semidetachment of the intervening skin. The burned area may show an increased redness for a week or more. No scars remain.

2. Lewis, T., and Grant, R. T.: Vascular Reactions of the Skin to Injury, Heart **11**:209, 1924.

Degree two is one of vesication. The epidermal cells have undergone a true coagulation necrosis, due to the conversion of their soluble colloids (sols) into the insoluble "pectous" modification.[3] An exudation of fluid passes from the tips of the papillae into the epidermal layers, where the cells which have been killed or injured by the heat, are swollen and soon dissolve completely. This passage of fluid has been attributed to the liberation in the skin of a diffusible substance having a histamine-like action on the minute vessels. It takes place at first immediately over the papillae, the interpapillary cells remaining intact for a while, until they are stretched, distorted and finally dissolved by the increasing volume of fluid exudate.[4] The serous exudation is accom-

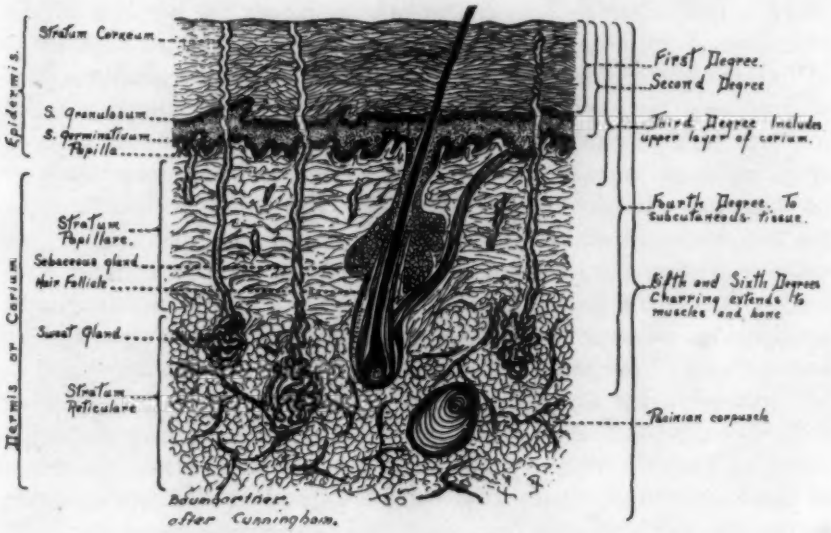

Fig. 1.—Dupuytren's classification of burn depth.

panied by an infiltration of mononuclear leukocytes. The rapidity of the exudation is dependent on the intensity of the stimulus, the sensitiveness and the vascularity of the part affected. In mild cases the various sized vesicles or collections of fluid remain within the epidermis, leaving the basal cell layer or stratum germinativum attached to the corium. In the more severe types, the fluid collects more rapidly and in greater amounts, beneath the epidermis, forming a bulla instead of a vesication. This bulla lies between the epidermis and corium. Macleod believes that the heat converts the moisture within the epidermis into steam,

3. Wells, H. G.: Chemical Pathology, Philadelphia, W. B. Saunders Company, 1918.

4. Ziegler, E.: A Text-Book of Pathological Anatomy, New York, William Wood & Company, 1887.

which separates the prickle cell layer, forming irregular spaces, facilitating the collection of serum. The volume of the vesicle varies from that of a pinhead up to that of an orange, their number usually being in inverse ratio to their dimensions. The size and extent of the bullae are dependent on their position in the skin, being larger in areas where the skin is thin and much less marked in proportion where the skin is thick.[5] When the death of the skin has been subsequent to the injury, dark sanguineous vesications may form as in ordinary gangrene.

The contents of burn blisters are variable.[3] Mörner found 5.03 per cent of proteins, which included 1.359 per cent of globulin and 0.011 per cent of fibrin.[6] Engel states that the amount of protein in blister fluids is proportional to the amount in the blood. Blister fluid may be either a transudate or an exudate, depending on the severity of the irritation. With a more intense stimulus, the capillary permeability is so altered that the fluid resembles plasma rather than serum. This plasma has a high and variable content of fibrinogen, which clots and converts the fluid into a fibrinous exudate. If this blister is not emptied of its contents, organization of the fibrinous exudate is more likely to occur than spontaneous absorption. The clear serum within the blebs becomes cloudy in twenty-four hours. A substance reducing copper oxide is present in an amount equivalent to 100 mg. of sugar per hundred cubic centimeters (author's analysis). Blister fluid contains antibodies of all sorts, including amboceptors sufficient for complement-fixation tests (Eisenberg, Buschke and Zimmerman).

Occasionally, if the vesicles are prevented from rupturing, the fluid content is absorbed, and epidermatization proceeds beneath the unbroken cuticle. When the blisters rupture due either to an accident or to a loss of elasticity with spontaneous breaking, a continuous discharge of serum occurs over the burned surface. The roof of the vesicle becomes a thin, wrinkled pellicle which is movable over the reddened tender base. When the cuticle is removed, the cutis vera, red and painful, is left exposed. If the serum is drained off, repair occurs quickly with covering of the corium by thin new epithelium. Scarring will not result if the corium is not involved, and infection remains absent. The burned area may remain red and pigmented for a month.

In the third degree the epidermis is completely destroyed and part of the corium, but the tips of the interpapillary processes remain intact. This is the most painful type of burn because the exquisitely sensitive terminal nerve filaments are left bare and exposed. The papillae of the skin appear as a reticular framework, containing serum, bits of per-

5. Daggette, A. S.: Burns and Their Treatment in General Practice, St. Louis Med. Rev. **51**:189-192 (March 11) 1905.

6. Mörner, K.: Skand. Arch. Physiol. **5**:272, 1895.

sistent living epithelium, leukocytes and masses of fibrin.[7] The papillae of the injured portion are visible as red points on a white ground. The subpapillary plexus of blood vessels and lymphatics absorb the toxins formed in the burned skin. Occasionally the sweat glands attempt to excrete these poisons, and a skin eruption occurs which simulates the rash of scarlet fever.[8] Tiny sudaminous vesicles may sometimes be found surrounding the burned area. The sebaceous and sweat glands and hair follicles are deep enough to remain uninjured, so that when the process of healing is inaugurated, each of these structures serves as a focus of potential epithelial growth, and the denuded area is quickly covered with new epithelium. The formation of this new skin requires from fourteen days to four weeks. The resulting scar is white, elastic, possessed of all the structural elements of true skin and undergoes no contraction.

Degree four involves destruction of the entire integument. In every burn there are two tissue layers to be considered: the dead or destroyed tissue and beneath this, the injured or sick tissue. In this degree of burn the skin has been disorganized by the heat; the tissues are mortified. The dead skin forms an eschar, which is brownish or blackish and dry like leather if produced by flame, or white, marble-like and coriaceous if burned by steam at high pressure.[9] The white or gray skin of the latter is due to the fact that blood cannot circulate through the vessels of the corium; consequently, the color changes normally produced by finger pressure will be absent. The eschar is insensible to touch. The eschar is depressed below the level of the surrounding skin, which is drawn in around it, showing puckered folds and corrugations radiating from the periphery of the disorganized area. The area about the eschar gradually shades off into hyperemic zones in which the burns are of the third, second and first degrees. In a short time an acute inflammatory process starts around the retracting eschar, and a groove results, intervening between the edges of the dead and living tissues. This is the initial step in sloughing, a process that ordinarily requires two weeks for completion, providing it is not hastened by intervention. The eschar occasionally is cracked or fissured, especially near the joints, where movement occurs, rupturing the dry and brittle skin. At times these fissures appear immediately after the injury, and the split skin extends down to the subcutaneous tissue. Here the fat cells of the panniculus adiposus lose their oily contents, due to

7. Kaposi, M.: Pathologie et traitement des maladies de la peau, trans. by Besnier and Dayon, Paris, 1891.

8. Colcord, A. W.: Burns, Internat. J. Surg. **34**:196-203 (June) 1921.

9. Ravogli, A.: The Management of Burns, J. A. M. A. **65**:291-295 (July 24) 1915.

melting by the heat, and the released fat flows out over the edge of the fissure on the surrounding skin. If any part of the corium remains, some of this fat may be disseminated throughout it in the form of small granular masses. It is astonishing that arteries and nerves sometimes preserve their vitality for several days in the midst of this disorganization.

The process of healing begins soon after the injury, but is not so evident until sloughing or mechanical removal of the dead skin occurs. The remaining débris is cleaned up or liquefied, partly by autolysis, partly by leukocytic digestion, and the residue either flushed off the surface of the wound or absorbed via lymphatics. In severe scalds of the hands and feet the nails may become detached. Infection and suppuration only too frequently accompany the separation of the necrotic tissue. The raw surface is covered with a fibrinous exudate, which exerts a chemotactic or thigmotropic influence on the growth of new tissue cells. The exposed ends of the blood vessels are closed by little plugs of thrombi, but from these capillaries, tufts of endothelial cells, accompanied by fibroblasts, grow out along the fibrinous framework and organize it into new tissue, known as granulation tissue. The sprouts of endothelial cells hollow out into tubes, forming new anastomosing capillaries, which arch and thereby gives the granular appearance to the surface of the new tissue.[10] The granulation tissue is in time covered by a thin bluish film of epithelium, which grows in from the periphery at the rate of one eighth of an inch a week. The new epidermis later becomes thicker and opaque. A good deal of contraction occurs, and scarring is inevitable. The scar by its cicatricial contraction is a common cause of deformity. The granulation tissue has a marked tendency to become overabundant and luxurious, a condition which hinders epithelialization, and makes the resultant scar irregular, inelastic, protuberant and contracted. The scar may be smooth and shiny due to the absence of such epidermal accessories as hair follicles and sweat glands. The border of the scar is irregular, indented and occasionally stellate.

In degree five the muscles are encroached on. There is no essential difference from a burn of the fourth degree, except that the surface is more deeply charred. The scar is deeper, firmer and immobile. There is greater disfigurement. Depending on the importance of the muscles involved, a considerable functional impairment may result. The scar has a decided tendency to break down and ulcerate.

In degree six the tissues are charred and carbonized, being converted by the heat into animal charcoal. The fingers and toes are the parts most frequently exhibiting this degree of destruction. A larger member

10. MacCallum, W. G.: A Text-Book of Pathology, ed. 3, Philadelphia, W. B. Saunders Company, 1924.

is seldom the seat of carbonization, unless the patient was insensitive, paralyzed or forcibly prevented from movement at the time of injury. The heat may fracture the bone.

GENERAL CHANGES

There are no internal or visceral lesions pathognomonic of burns and scalds. As early as 1840, Long noted that the pathologic changes in the internal organs closely resembled those due to acute febrile diseases involving the skin.[11] The toxin of burns is cytotoxic for parenchymal cells. Many investigators have attributed a goodly portion of the visceral pathology to minute capillary thrombi.[12] These tiny thrombi are assumed to be distributed ubiquitously throughout the body and by their plugging action, which occurs during life, produce a stasis and hyperemia in the lungs, kidneys, gastro-intestinal tract, brain, liver, etc.[13] Thrombosis is a beneficial and protective process when it seals the oozing blood vessels in the burned area, because this prevents the dehydration of the blood and in some degree the absorption of toxins, but the same process within the viscera is wholly undesirable. I think that thrombosis is not nearly as important a factor as the earlier pathologists believed, and that many of the visceral changes can be attributed to a thick, viscid, concentrated blood. Brown-Séquard believed that the various remote effects produced by burns were brought about through the medium of the spinal cord, which he regarded as reflecting the irritation from the burnt part to the secondarily affected organs.

When a burn undergoes an exhaustive suppurating process, the amyloid infiltration of viscera, which so commonly follows chronic destructive infections, is likely to ensue.

The Nervous System.—Necropsy reveals hyperemia of the brain and meninges. There may be an effusion of blood between the dura mater and the bone. The white substance displays puncta vasculosa. The arachnoid vessels may be engorged with blood and contain occasional thrombi. Korolenko states that the sympathetic nervous system is seriously involved. The cerebral cortical cells and ganglion cells are uninjured except in instances of shock, in which the nerve exhaustion is accompanied by chromatolysis or partial destruction of Nissl's granules (Crile).

Lungs.—Within fifteen minutes after the occurrence of the injury, an eosinophilia appears in the lungs, but this is not specific because it is found subsequent to all destruction of animal tissue, resulting in endo-

11. Long: London Med. Gaz. **1**:743, 1840.

12. Baraduc: Union méd., Paris, May 19, 1863.

13. Silbermann: Centralbl. f. d. med. Wissensch. **27**:513, 1889; Arch. f. path. Anat. u. Physiol. u. f. klin. Med. **119**:488, 1890.

genous intoxication (Kotzareff). The lungs are congested and may contain fibrinous plugs. Thrombi have been reported in the small branches of the pulmonary artery, obstructing the circulation and exerting additional strain on the right ventricle.

Kidney.—The tissue toxin, being secreted by the kidney, produces an acute glomerulitis. Cloudy swelling and fatty degeneration later appear in the proximal convoluted tubules. The degeneration is accompanied by venous stasis which induces further tissue breakdown.[14] Wertheim found thrombi in the kidney, occurring most abundantly in the capillary tufts of the glomeruli.[15] With severe burns, necrotic foci become abundant in the kidney and grow larger and more extensive as the toxemia persists. These necrotic areas incite cell multiplication, and a proliferative process results, with irreparable damage to the kidney. Hemoglobin pigment is found in the kidneys, being most abundant in the straight uriniferous tubules, although occurring also within Bowman's capsule and the convoluted tubules. This blood pigment is responsible for the dark brownish red color of the kidneys, as described in necropsy reports, and which has erroneously been attributed to excessive hyperemia. This hemoglobin is excreted through the glomeruli and appears in the urine.

The Suprarenal Glands.—H. C. Weiskotten has made an intensive study of the pathology of the suprarenal gland in extensive burns.[16] Whereas the normal weight of the suprarenal gland is from 4 to 7 Gm., in burned patients its weight is often from 20 to 25 Gm. The perisuprarenal fat tissue is markedly edematous. The suprarenal gland of the young patient is more labile, with reference to the burn toxin, than is the adult gland. The glands are swollen and deep red, due to hyperemia and ecchymotic areas of hemorrhage among the parenchymal cells. These pathologic changes are more or less in direct proportion to the extent of the burned lesion. The gland cells are swollen, pale staining, hydropic and frequently necrotic. The type of changes in the suprarenal is similar to that occurring in diphtheria intoxication and antiphylactic and peptone shock. On analysis, the epinephrine content is low or totally absent.[17]

Heart.—Necropsy occasionally reveals subendocardial and subepicardial hemorrhage. If the toxemia has persisted for a sufficient length

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14. Turck, F. B.: Kidney Lesions Produced by Tissue Breakdown. Pathogenesis and Treatment, Am. J. Surg. **37**:129, 1923.

15. Wertheim: Wien. med. Presse **8**:1237, 1867.

16. Weiskotten, H. G.: Fatal Superficial Burns and the Suprarenals, J. A. M. A. **69**:776 (Sept. 8) 1917; Histopathology of Superficial Burns, ibid **72**:259 (Jan. 23) 1919.

17. Olbrycht, J.: Rev. de méd. **41**:81, 1924.

of time, the cardiac musculature exhibits areas of hyaline and fatty degeneration and necrosis of the muscle fibers. It is possible for the right ventricle to be dilated.

Liver.—Hyperemia, focal necrosis and parenchymatous degenerative lesions form the characteristic pathologic picture in the liver.

Spleen.—The spleen is softened and enlarged. Focal necroses occur in the germinal centers of the lymph nodules or malpighian bodies. The lymphoblasts undergo karyorrhexis and karyolysis, and are rapidly ingested by phagocytic endothelial leukocytes. The latter cells may proliferate so rapidly that they completely fill the germinal centers and are bordered peripherally by a narrow rim of lymphocytes. The endothelial leukocytes may fuse to form foreign body giant cells. These lesions reach the height of their development within seventy-two hours after the injury. Later the lymphoid nodule appears homogeneous, due to hyaline degenerative changes.[18]

Lymph Glands.—Bardeen has described certain lesions occurring in all the lymphoid structures throughout the body, lymph glands, spleen, intestinal follicles, etc.[18] The germinal center of the follicle is first edematous. Swelling and distortion of the lymph cells of these areas are soon followed by necrosis and dissolution, the changes gradually extending peripherally. The clearance of this lymphocytic débris from the center of the follicle discloses large, flat endothelial cells containing faintly staining nuclei. McCrae states that the proliferation of these phagocytic endothelial cells is identical with that seen in typhoid fever and other acute infections.[19] Flexner suggested that the focal pathologic effects resulting from the action of toxins within the body might be due to certain peculiar relations of the capillary circulation.[20] Bardeen explains the lymphatic necrosis in burns on the same assumption. The toxin exerts its initial deleterious action on the center of the follicle because of the vascular arrangement of this follicle. This arrangement is such that a tiny arteriole runs to the center of this area and here breaks up into capillaries which radiate out from the center and are collected into veins at the periphery of the follicle. These anatomic studies were the work of Calvert. These lesions are almost similar to the ones produced by an experimental injection of diphtheria toxin into animals. Kolosko interpreted these findings in severe burns as being due to a hemorrhagic infarction of the lymph glands.[21]

Bone Marrow.—Necropsies on human subjects and on dogs, experimentally burned, reveal focal necroses of the bone marrow, if the subjects

18. Bardeen, C. R.: J. Exper. Med. **2**:501, 1897.
19. McCrae, J.: Tr. Ass. Am. Phys. **16**:153, 1901.
20. Flexner: J. Exper. Med. **2**:213, 1897.
21. Kolosko: Vrtljschr. f. gerichtl. Med. **47**:217, 1914.

live long enough to permit the start of an active leukopoeisis.[22] Burn toxin in mild amounts is positively chemotactic for leukocytes and stimulates the bone marrow to increased productive activity, but like many other irritants, an excessive quantity destroys instead of stimulates.

Gastro-Intestinal Tract.—The primary lesions of the gastro-intestinal tract commonly caused by caustics will not be considered here, but only the pathology secondary to burns and scalds of the skin. The intussusception of the small intestine so commonly mentioned as a necropsy finding is probably of postmortem origin. The swelling and pathologic changes of the solitary and agminated lymph nodules are similar to the lesions described by Bardeen in other lymphoid structures.[23] There is a generalized hyperemia of the mucous membrane, with punctate areas of petechial hemorrhage into the mucous membrane of the stomach and intestines, particularly in the ileum near the cecum. The ecchymosis may be large and at times produce an ulceration. The overemphasized duodenal ulcer will be considered in detail under the complications of burns.

Serous Cavities.—The pleural, peritoneal and joint cavities are prone to contain an accumulation of serous exudate, especially when the burn or scald is of the skin overlying the serous cavity.[24] The exudate is occasionally hemorrhagic.

THE BLOOD AND URINE

Red Blood Cells.—The erythrocytes undergo extensive alterations in morphology and function. There is considerable variation in the form of these cells, some being spherical, others bell-shaped and still others crenated, probably due to a partial melting of the lipoid capsule of the red blood cells by the heat.[25] Distortion is more common than fragmentation and solution, although infrequently the red blood cells are broken up into globules or granules. Occasional ghost or shadow cells are seen.[26] The hemoglobin may be gathered in circumscribed masses in the cell. The erythrocytes sometimes contain basic staining granules. Schultze experimented on animal blood, demonstrating that when it was exposed to a temperature of 52 C. the red blood cells broke up into spherical bodies, which lost their hemoglobin.[27] Moreover, there exists a considerable diminution in the vital properties of the

22. Foà: Riv. Sper. di freniat. **7**:135-143, 1881.
23. Avdakoff: Dissertation, St. Petersburg, 1876.
24. Cumin: Edinburgh M. & S. J. **19**:337, 1823.
25. Sahli, H.: Treatise on Diagnostic Methods, Philadelphia, W. B. Saunders Company, 1914.
26. Ewing, J.: Clinical Pathology of the Blood, ed. 2, New York, Lea Bros. & Co., 1903.
27. Schultze: Arch. f. microscop. Anat. **1**:1, 1865.

erythrocytes [28] as noted by their lowered resistance to such influences as heat, compression, drying, salt solutions and staining.[29] In severe but not fatal cases, there is an immediate increase (within a few hours) in the number of erythrocytes from 1,000,000 to 2,000,000 per cubic millimeter of blood. In fatal instances the increase is often from 2,000,000 to 4,000,000 per cubic millimeter of blood.[30] This apparent increased number of red blood cells is due to a partial paresis of the vasomotor system and to a venous stasis induced by blood concentration following a loss of plasma from the blood vessels. When this blood concentration returns to normal, a secondary anemia begins.[31]

White Blood Cells.—There is considerable destruction of leukocytes in patients suffering from severe burns. Immediately after the burn, a rapidly rising leukocytosis ensues, reaching 30,000 per cubic millimeter of blood in severe cases and 50,000 in fatal cases. A differential white blood cell count shows that the percentage of neutrophilic polymorphonuclears is increased to 80 or 85 per cent of the total number of leukocytes. It is obvious that the percentage of neutrophils is less than in inflammatory leukocytosis of infectious origin. Myelocytes are present in small numbers in severe cases. A late appearing leukocytosis may be due to infection of the burned area.

Blood Platelets (Thrombocytes).—Welti and Locke usually found the blood platelets markedly increased,[32] whereas Salvioli states that they are diminished in the blood plasma in direct proportion to the severity of the lesion. He believes the reason for their lessened number lies in their agglutination to form thrombi.[33]

Thrombosis.—In burns and scalds a predisposition to thrombosis exists because of the leukocytic disintegration, the venous stasis and the viscidity of the concentrated blood. The coagulation time of the blood (Dorrance-Bransfield coagulometer) is decreased as low as two minutes in some instances. Three kinds of thrombi are present: (*a*) fibrin thrombi (ferment thrombi); (*b*) thrombi composed mostly of blood platelets, and (*c*) thrombi from precipitation (thromboses par precipi-

28. Lesser, V.: Arch. f. path. Anat. u. Physiol. u. f. klin. Med. **79**:248, 1880; Arch. f. Physiol., Leipzig, 1881, p. 236.

29. Silbermann: Glasgow M. J., May, 1892.

30. Locke, E. A.: Boston M. & S. J. **147**:480 (Oct. 30) 1902.

31. Dorrance, G. M., and Bransfield, J. W.: Surg. Clin. N. Am. **2**:299 (Feb.) 1922.

32. Welti: Beitr. z. path. Anat. u. z. allg. Pathol. **4**:521, 1889; Centralbl. f. allg. Path. u. path. Anat. **1**:537-550, 1890.

33. Salvioli: Arch. per la scienze méd. Torins et Palermo **15**:157, 1891; Arch. ital. de biol. **15**, 1891; Arch. f. path. Anat. u. Physiol. u. f. klin. Med. **125**:364, 1891.

tation).[34] The fibrin thrombi are caused by liberation into the blood of tissue elements set free in the areas of the burn lesions or to substances set free by the direct destruction of the blood.

Blood Concentration.—In extensive superficial burns involving considerable areas of the body surface, a rapid pouring out of fluid on the surface of the body occurs; or if the skin is intact, the part affected becomes edematous with extreme celerity. The rapid and continuous loss of fluid from the blood in burned patients quickly induces a marked concentration of the blood. "Marked concentration of the blood means a failing circulation, an inefficient oxygen carrier, oxygen starvation of the tissues, fall of temperature, and finally, suspension of vital activi-

TABLE 1.—*Classification of Burned Patients. Initial Values for Hemoglobin* *

	Hemoglobin	
	In Percentage	In Percentage of Normal †
Group 1: Seriously Burned		
Patient 1	174	158
2	230	209
3	200	181
4	167	151
5	167	151
6	167	151
7	153	137
8	174	158
9	170	154
10	205	186
11	164	149
12	167	151
13	200	181
14	156	138
15	167	151
Group 2: Less Seriously Burned		
Patient 16	129	117
17	150	136
18	130	118
19	129	117
20	135	122
21	130	118

* Underhill, Carrington, Kapsinow and Pack: Arch. Int. Med. **32**: 31 (July) 1923.
† Assuming the normal reading (Cohen-Smith method) to average 110.

ties."[35] The degree of response to the injury with respect to the local disposition of tissue fluid is in direct ratio to the extent of the injury. The fluid lost from the blood partakes of the nature of plasma and contains significant quantities of blood proteins, particularly fibrinogen. The direct cause of blood concentration is due to a changed permeability of the capillary wall, brought about by the more or less specific action of the burn toxin on the capillaries, resulting in a pouring of fluid into the tissue spaces of the body.

34. Hayem: Du sang et de ses altérations anatomiques, Paris, 1889; Wien. med. Ztschr. 1897, nos. 17-19.

35. Underhill, F. P.; Carrington, G. L.; Kapisnow, R., and Pack, G. T.: Blood Concentration Changes in Extensive Superficial Burns, Arch. Int. Med. **32**:31 (July) 1923.

The hemoglobin readings of the blood are assumed to be the measurements of relative blood concentration. The more extensively burned patients responded with a greater concentration of the blood.

The Composition of the Blood.—The changes observable in the composition of the blood during burns vary at most only slightly from the normal limits. Any quantitative increases noted cannot be interpreted as evidences of absorption of unusual products of protein breakdown, but are rather to be regarded as the expressions of the change that would be expected in blood highly concentrated. The data on sodium chloride content of the blood plainly indicate that this salt played a significant rôle in fluid interchange. The sodium chloride values vary inversely with those for hemoglobin. The gases of the blood are markedly diminished, but the blood possesses the ability of taking up oxygen in large amounts.[36] Some hemoglobin may be in free solution

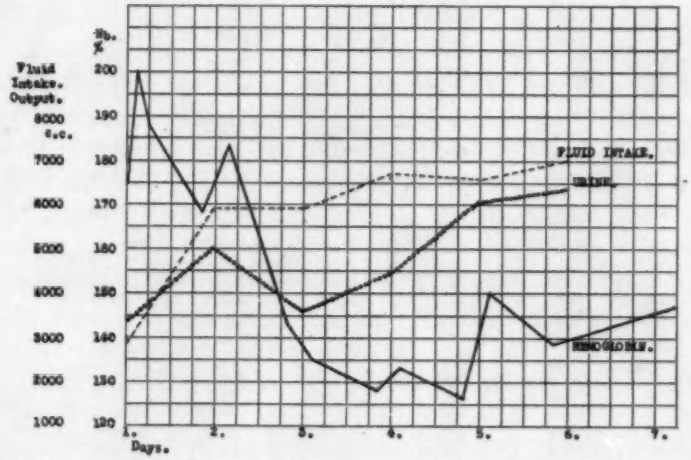

Fig. 2.—The relationship of blood concentration to fluid intake and urine output (Underhill, Carrington, Kapsinow and Pack: Arch. Int. Med. **32**:31 [July] 1923).

in the blood plasma but no derivatives of hemoglobin, that is, no bilirubin, biliverdin or methemoglobin.[37]

The Urine.—Severe burns cause an oliguria because of two factors, kidney lesions impairing the renal secretion and a concentrated blood with insufficient plasma to exert an hydremic stimulus on any kidney. The urine is highly colored and often smoky because of the hemoglobinuria. The specific gravity is naturally increased. Albumin appears very soon after the reception of severe and even of almost immediately fatal burns. In burns of mild degree only a faint trace of albumin

36. Roger and Guinard: Semaine méd., Nov. 3, 1894.
37. Hoppe-Seyler: Ztschr. f. physiol. Chem. **5**:1-9, 1881.

is present on the first day, but it increases in amount on subsequent days. With each exacerbation of fever, albumin again appears. Acetonuria frequently appears by the third day after the burn. Various investigators have written of the presence of a protein of unidentified character in the urine of patients after severe burns.[38] Wilms noted an albumosuria as a common occurrence.[39]

TABLE 2.—*Composition of the Blood in Severely Burned Patients* *

Case	Date, 1921	Nonprotein Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Creatine, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Urea, Mg. per 100 Cc.	Chloride as Sodium Chloride in Percentage
1	Nov. 28	38.72	2.23	9.68	166.1	17.90	....
	Nov. 29	34.96	3.26	8.34	177.9	.....	....
	Nov. 30	36.08	2.14	17.65	172.4	16.14	0.37
2	Nov. 28	48.12	1.70	11.50	216.4	16.50	....
	Nov. 29	63.60	3.26	9.37	194.2	27.02	0.31
	Nov. 30	37.00	2.20	7.69	174.8	19.30	0.34
	Dec. 1	41.52	2.14	13.10	181.1	20.14	0.43
3	Nov. 28	38.52	1.59	.....	133.3	.....	....
	Nov. 29	35.24	2.59	7.60	135.8	15.42	....
	Nov. 30	27.92	1.87	14.29	146.1	15.86	0.37
4	Nov. 28	37.48	1.70	12.50	121.6	.....	....
	Nov. 29	36.13	3.26	7.70	97.8	15.30	0.44
	Nov. 30	33.72	2.14	14.63	181.1	19.68	....
5	Nov. 28	36.84	1.63	14.28	138.8	.....	0.47
	Nov. 29	33.76	2.14	15.00	158.7	.....	0.41
	Nov. 30	31.00	1.92	15.42	149.7	14.80	0.43
6	Nov. 28	42.64	1.59	9.20	133.6	9.42	0.44
	Nov. 29	41.84	3.41	14.63	116.8	.....	....
	Nov. 30	34.92	2.20	16.60	162.3	12.82	0.37
	Dec. 1	38.96	1.92	6.20	117.6	.....	....
7	Nov. 28	36.40	1.78	9.50	117.0	14.32	....
	Nov. 29	33.48	3.00	7.70	99.4	8.72	....
	Nov. 30	30.28	2.02	16.20	128.2	16.72	....
	Dec. 1	37.24	2.14	12.50	132.9	16.86	0.40
8	Nov. 28	55.32	1.74	14.29	199.2	22.98	0.33
	Nov. 29	50.48	1.97	12.00	181.8	30.16	....
9	Nov. 28	34.72	1.87	9.23	133.3	.....	0.54
	Nov. 29	31.64	3.00	7.50	122.5	.....	....
	Nov. 30	31.08	1.97	13.95	181.1	13.06	0.39
	Dec. 1	36.72	2.82	12.00	139.6	16.32	0.36
10	Nov. 28	38.24	2.27	10.16	173.2	16.24	....
	Nov. 29	39.04	2.59	8.70	120.4	16.26	....
	Nov. 30	38.40	2.20	11.75	138.8	14.08	....

* Underhill, Carrington, Kapsinow and Pack: Arch. Int. Med. **32**: 31 (July) 1923.

THE POISONS PRODUCED IN BURNS AND SCALDS

The poisons elaborated in burns and scalds evidently may originate from two sources: directly through destruction of the tissue and blood, and indirectly by disturbing the functions of the skin and internal organs. The skin exhales no harmful products. The amount of skin destroyed in nonfatal burns and scalds is insufficient to interfere seriously with the excretion of a normal quantity of sweat, because the remain-

38. Becky, K., and Schmitz, E.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **31**:416, 1919.

39. Simon, C. E.: A Manual of Clinical Diagnosis, ed. 8, Philadelphia, Lea & Febiger, 1914.

ing uninjured skin can easily compensate by an increased activity. The deleterious effects resulting from varnishing the total skin area of animals are not due to the retention of noxious materials or absorption of altered skin metabolites, but to an increased heat loss and hypothermia.[40] The excretion of waste materials is one of the least important of the skin's many functions. The noxious retention theory of the toxemia of burns is no longer tenable.

A toxemia is practically always in evidence after serious burns and scalds, as recognized by the symptomatology and necropsy findings. The fever of uninfected burns is no doubt due to the action of the released toxin on the medullary heat center. There are two important facts to be ascertained about this toxin: Where does it originate? What is its chemical nature or composition?

Is the toxin formed from injured blood elements or is it a product of the burned tissues? Scholz is of the opinion that the blood itself rather than the tissues is the seat of chemical change.[41] Ravenna and Minassian assert that blood heated in vitro to 55 or 60 C. is toxic and on injection produces identical visceral lesions with the burn toxin, whatever it may be. Numerous investigators have agreed that a toxin circulates in the blood of burned patients, but state that it cannot be detected by known chemical means.[42] Pawlowsky denies the presence of a toxin in the blood.[43] The presence of the toxin in the blood does not necessarily indicate its formation there any more than its detection in the urine establishes this fluid as the toxicogenic substance.

The present consensus of opinion favors the burned tissue as the source of the toxin, which is absorbed and circulates in the blood,[44] being carried by the red blood corpuscles.[45] Some ingenious and clever experiments have been devised to demonstrate the source of this hypothetical toxin. Just as the immediate excision of crushed muscle tissue will prevent the occurrence of shock, so will the early removal of burned tissue exempt the patient from toxemia. Vogt demonstrated the foregoing experiment on animals. If burned areas of equivalent size and severity were permitted to remain for eight hours, the animals invariably died; but the transplantation of this burned skin to a normal animal

40. Stewart, G. N.: A Manual of Physiology, New York, William Wood & Company, 1918.

41. Scholz, E.: München. med. Wchnschr., Jan. 30, 1900.

42. Boyer and Guinard: Des Brûlures, Paris, 1895. Spiegler, E.: Wien. med. Bl. **19**:259, 277, 294, 310, 1896; Mracek: Handbuch der Hautkrankheiten **2**:95, 1905; Wertheim: Wien. med. Jahrb. 1868, p. 37.

43. Pawlowsky, A. D.: Atti. d. XI. Cong. Med. Internaz. (1894) Roma Chirurg. **4**:267-269, 1895.

44. Pfeiffer: München. med. Wchnschr. **61**, June 16, 1914.

45. Willis, A. M.: Editorial, Surg. Gynec. & Obst. **39**:834 (Dec.) 1924.

resulted in the latter animal becoming toxic within an hour, while the burned animal was saved from a toxic death by the transplantation.[46]

Confirmatory evidence has been given by parabiosis (artificial union of a pair of animals by operative procedure, so that their blood mingles). When one of these animals is burned the other becomes intoxicated also, and the burned animal suffers less than would ordinarily be the case. If the united animals are separated within twelve hours after one is burned, the unburned animal does not develop toxic symptoms (Vogt). Heyde and Sauerbruch verified these parabiotic experiments. Hyde utilized this principle in disproving the theory of reflex action.[47] Vaccarezza demonstrated that the blood was the vehicle for the poisonous substance by experiments in which the leg of a dog was burned and then the femoral artery flushed with physiologic sodium chloride until the fluid coming from the femoral vein returned clear. Then he sutured the femoral artery to the central stump of the carotid in a second dog *B* and the femoral vein of *A* with the jugular vein of *B*. Consequently, the burned limb was irrigated solely with the blood from dog *B*, practically none getting into the general blood stream of dog *A*. Dog *B* died while dog *A* survived.[48]

Salvioli, Markusfeld and Steinhouse found that after cutting off the blood supply to a rabbit's ear, a burn of this ear would evoke no constitutional disturbance; but if the nerves to the ear are severed and the blood supply left intact, toxemia results. Cannon substantiated his theory that shock was due to an intoxication with protein cleavage products, by a series of experiments in which he crushed the muscles of dogs whose legs were constricted by tourniquets, and found that shock was delayed until the tourniquets were removed.[49] It is evident from these similar instances that the poisonous substance is generated or elaborated in the injured tissue and cannot cause a generalized toxemia until it has been absorbed and circulated by the blood. Perhaps this is one explanation why an extensive superficial burn is more dangerous than a small deep one.

These experiments are sufficiently uniform and conclusive to accept the burned tissue as the origin of the poison. Eijkman and Hoogenhuyze, by asserting that the burning of muscle was not followed by intoxication, created the erroneous impression that the skin was the sole source of this hypothetical poison. The prolonged treatment of an inoperable carcinoma of the cervix by low heat (Percy's "cold iron"

46. Vogt, E.: Ztschr. f. exper. Path. u. Therap. **11**:191, 1912; quoted by Wells, H. G.: Chemical Pathology.

47. Heyde, M.: Med. Klin., Feb. 18, 1912.

48. Vaccarezza, R. A.: Rev. Soc. méd. Argentina, Buenos Aires **35**:207-210, 1922.

49. Cannon, W. B.: Studies in Experimental Traumatic Shock, Arch. Surg. **4**:1 (Jan.) 1922.

method) resulted in a rapidly fatal outcome with lesions similar to those in cases of fatal cutaneous burns (Leonard and Dayton).[50] This aids in proving that the source of the burn toxin is not necessarily in the skin. Moreover, it has been more recently shown that burning of muscle and of subcutaneous tissue is followed by systemic poisoning.[51]

The symptoms of toxemia do not appear until after the first twenty-four hours, a fact which indicates, according to Robertson and Boyd, that the damaged tissue must be in contact with living tissue for some time before a toxic substance can be manufactured. The paradoxic occurrence of mild symptoms and quick recovery from a burn that according to normal laws would be lethal, has been explained by a presumable hindrance in absorption facility, or the continued and excessive high heat has destroyed the poison. The variation in individual resistance to burns is due to a decreasing or increasing natural immunity to the patients' own tissues (Turck).

The toxins are eliminated by the kidneys and intestines in which they produce lesions while in transit. The kidneys excrete these poisons [52] in quantities sufficient to make the urine of increased toxicity to rabbits.[53] The urine of burned patients and animals contains an increased non-specific proteolytic ferment, which is capable of splitting glycol-tryptophane (Pfeiffer).[54]

Every conceivable substance that could be formed in the intermediary metabolism of the body has been suggested as the poison responsible for the toxemia of burns. Some of these are listed herein:

1. A toxin causing lesions similar to the ones produced by abrin and ricin (Stengel and Fox).

2. A toxin causing lesions similar to the ones produced by diphtheria toxin (Weiskotten).

3. A toxin allied to the ones produced in secondary wound shock and intussusception, but differing from these in that it causes convulsions (Robertson and Boyd).

4. Hydrocyanic acid formed in the skin. Sweat contains formic acid. The neutralization of this acid on the skin by ammonium hydroxide forms the very soluble ammonium formate salt. When this salt is heated it loses water and becomes hydrocyanic acid (Catiano).[55]

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50. Leonard, V. N., and Dayton, A. B.: Fatal Complication of Percy's "Cold-Iron" Method in the Treatment of Inoperable Carcinoma of the Cervix, Surg. Gynec. & Obst. **24**:156 (Feb.) 1917.

51. Robertson, B., and Boyd, G. L.: J. Lab. & Clin. Med. **9**:1-14 (Oct.) 1923.

52. Spietschka: Ueber Verbrennungen und Verbrennungstad, Arch. f. Dermat. u. Syph. **103**, nos. 1-3.

53. Reiss: Wien. med. Wchnschr. **43**:59-61, 1893.

54. Ferrae: München. med. Wchnschr. **61**:1287.

55. Catiano: Ueber die Störungen nach ausgedehnten Hautverbrennungen, Virchows Arch. f. path. Anat. **87**:345-364, 1882.

5. Potassium salts set free by destroyed erythrocytes (Schjerning).[56]

6. Ammonia accumulation in the blood (ammonemia).

7. Methyl guanidine (Kutcher and Heyde).[57]

8. Pyridine base (Reiss).[58]

9. Lactic acid and carbon dioxide (metabolites).

10. Amino acids; various individual ones.

11. Tyramine.

12. Hemolysins and hemagglutinins (von Dieterrichs,[59] denied by Pfeiffer and Burkhardt). Any hemolysis that occurs is probably due to the direct action of the heat on the blood as it circulates through the burned area rather than to specific antibodies in the blood serum.

13. A toxin which resembles in action the unknown poison in uremia (Pfeiffer).

14. Muscarin or a similar ptomain-like substance that is produced by bacterial action on the burn eschar (Lustgarten).[60]

15. Ptomaines produced in the burned tissues and appearing in the blood and urine (Anjello and Parascandolo).[61]

16. Histamine. Abel found histamine in many normal tissues of the body. Numerous pathologists have suggested that the burns and scalds released the histamine from the tissues.

17. Toxalbumin (Dorrance and Bransfield).[51]

18. Peptotoxins (Kijanitzin).[62]

19. Pathologic cleavage products of body proteins (Fraenkel and Spiegler).[63]

20. A nonprotein of intracellular origin. Utilizing charred tissue, burned to a crisp, and thereby having all organic matter destroyed, Turck caused toxemia and death in from six to twenty-four hours by injecting an aqueous suspension into animals.[54] Turck concludes that the toxin cannot be of organic nature. Although a scald does not char tissue, yet the same poison is active, because moist heat causes extrusion of the cellular toxin from the cells. Some cells release the toxin quicker than others.

21. A toxin of neucleoprotein composition and properties resembling snake venom. Pfeiffer believes this poison is of two different kinds: a thermostabile neurotoxic poison and a thermolabile necrogenic poison. He lists some of the characteristics of this poison as follows: it is weakened on standing in solution; it is weakened by sunlight; it can be absorbed from the gastro-intestinal tract; it is soluble in water, alcohol and glycerol; it is insoluble in chloroform and ether; it is nonvolatile.[64]

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56. Schjerning: Eulenb. Vljahr. f. gericht med. **41,** 1885; **42,** 1887.

57. Kutcher and Heyde: Centralbl. f. Physiol. **25**:441, 1911.

58. Reiss: Arch. f. exper. Path. u. Pharm. **51**:18, 1904.

59. Von Dieterrichs: Wien. med. Wchnschr., Nov. 21, 1903.

60. Lustgarten: Wien. klin. Wchnschr. 1891, no. 29, pp. 528-531; Med. Rec. **40**:152, 1891.

61. Anjello and Parascandolo: Wien. med. Wchnschr, 1904, nos. 14, 15, 16.

62. Kijanitzin: Virchows Arch. f. path. Anat. **131**:436-467, 1893.

63. Fraenkel, S., and Spiegler: Wien. med. Bl., 1897, no. 5.

64. Pfeiffer: Virchows Arch. f. path. Anat. **180**:367, 1905.

22. Primary and secondary proteoses. Robertson and Boyd[64] have conducted some very thorough and complete experiments. They found that blister fluid and blood serum were innocuous and nontoxic. Whole blood was markedly toxic for guinea-pigs when 2 to 3 cc. were injected intraperitoneally, whereas 15 cc. of normal blood produced no symptoms. Fourteen cubic centimeters of cerebrospinal fluid, from a child suffering with severe toxemia, injected into a guinea-pig was poisonous. When blood was dialyzed against water through parchment paper, the diffusate was nontoxic and the residue toxic. Normal skin burned postmortem was not poisonous. The poisons generated in the burned skin are of two types: (1) a thermolabile necrotoxin, destroyed by boiling, nondialyzable, giving a positive biuret test, and not coagulated by heat, nitric or picric acids; and (2) a thermostabile neurotoxin, which will dialyze. These poisons are able to pass through a bacteria tight filter. Salting out of the extract of burned skin gave primary and secondary proteoses. The diffusate or neurotoxin contained only secondary proteoses.

23. Albumoses, which cause antiphylaxis. Small burned areas sensitize animals to further injections of burned tissue (Heyde).[47]

24. Antiphylaxis. It is a common experience of physicians to have their patient (usually a child) convalescing nicely for a week or twelve days, then suddenly become profoundly ill, with subnormal temperature, which occasionally progresses to convulsions, delirium and death. Tuder[65] explains this phenomenon as the occurrence of anaphylactic shock resulting when an adequate sensitization of the body has been formed against the continuously absorbed antigen.

In conclusion, we may state that the very complexity and multiplicity of the theories adumbrated above speak volumes for our ignorance of the true nature of the burn toxin, and stamp this evidence as nugatory. The toxin of burns is unknown.

BURN COMPLICATIONS

The most common complication of burns and scalds is a secondary pyogenic infection of the burned area. The heat or heated substance causing the burn sterilizes the skin and tissues, so that all lesions of this sort are primarily sterile. This sterility is short-lived, however, because the extensiveness of the lesion and the conditions attending the accident practically insure contamination. The dead and devitalized tissues offer a most suitable soil or nidus for the growth and development of bacteria. Practically every burn is infected within a few hours, but the infection is not necessarily clinically manifest until the necrotic tissue begins to slough away. The infection is always mixed, the organisms usually being *Streptococcus pyogenes, Staphylococcus aureus* and *Bacillus pyocyaneus,* although *Bacillus fetidus, B. subtilis, B. proteus* and other saprophytes are occasionally found. Suppuration begins and is the result of three factors: (1) cell necrosis, (2) local accumulation of leukocytes and (3) digestion of the necrotic cells, fibrin and tissue elements by ferments derived from leukocytes, the invading bacteria and

65. Tuder, T. J.: Internat. J. Surg. **28**:282 (Aug.) 1915.

the fixed tissue cells. Suppuration hastens sloughing. The sepsis is early and easily recognized by its peculiar and distinctly mephitic odor. In the early stages of the burn the bacterial count is high and the discharge profuse and seropurulent. The number of bacteria diminishes as the granulation tissue forms. From gross appearance alone, it is sometimes impossible to tell whether the granulations are sterile or infected. Furthermore, distinction must be made between a clinically and a bacterially sterile wound, and this can be ascertained only by a bacterial count. Pale, sluggish and inactive granulations are frequently due to some underlying constitutional defect or derangement such as syphilis (Sherman).[66] Adenopathies are found in the regional lymph glands draining the suppurating area.

Septicemia is a dangerous sequel to an infected burn. Erysipelas and pyemia are other complications. The intact skin may exhibit a peculiar rash which is almost similar to this feature of scarlet fever. Tetanus is more serious and common in burns of the head and trunk. The dead eschar is an excellent anaerobic culture medium for the tetanus bacillus. Newberger[67] reported two deaths from tetanus following burns in children, and collected instances occurring in forty-nine others.

Hemorrhage from superficial veins occurs in about 2 per cent of burns. The veins of the upper extremity are most commonly affected. Arterial hemorrhage is rare in burns because the large arteries are protected by the overlying strong fasciae, which are seldom burned through. The hemorrhage takes place at the time of sloughing, because of the inclusion of a blood vessel in the sloughing eschar.

Pregnant women are liable to abort, miscarry or enter premature labor after severe burns and scalds. The premature expulsion of the fetus or embryo occurs from the fifth to the seventh day after the infliction of the burn.

Meningitis (see general pathology) is not a common lesion, but leptomeningitis has followed burns of the head in rare instances. Apoplexy is occasionally a fatal termination in patients whose arteries are already sclerosed or who suffer from hypertension, the vascular excitement of the toxemia on the fifth or seventh day of the injury being sufficient to bring about rupture of the weakened arterial wall.

Bed sores frequently develop on the salient points of the sacrum, back and heels because of long-continued pressure.

Burns of the thoracic wall produce local and internal damage. A mastitis may occur, especially in lactating breasts. Destruction of the nipples by the burn is the most common cause of acquired athelia. Bronchitis and pneumonia result either from inhalation or indirectly

66. Sherman, W. O.: Surg. Gynec. & Obst. **26**:450 (April) 1918.
67. Newberger, C.: Am. J. Dis. Child. **6**:35 (July) 1912.

from surface injury of the chest, although Pearse insists that the elimination of toxins through the lungs is responsible for the pulmonary and pleural pathology. Pneumonia is more frequent after burns of the chest than after burns in any other area of the body.

The exhaustion and weakened powers of resistance in extensive burns permit the development and early fatal issue of pulmonary tuberculosis. Hall reported three instances of pulmonary tuberculosis, each one of which originated in a lung prevented from proper expansion by unilateral contraction of the chest wall, on the same side, originating from a scald acquired in infancy.[68] Schjerning and Seeliger present statistics showing lung complications 87 times in 125 dissections.[69]

Amyloid infiltration of the viscera is a sequel to prolonged suppuration and delayed healing of burns. Nephritis is a common complication, as has been previously emphasized. Peritonitis is more common after infected burns of the abdominal wall.

The Duodenal Ulcer of Burns.—In 1842, Curling read a paper before the Royal Medical and Chirurgical Society, "on acute ulceration of the duodenum in cases of burns."[70] This lesion was soon accepted as a common complication of burns and came to be known as "Curling's ulcer." Sir Berkeley Moynihan claims priority for Long of Liverpool, who described the ulcer in 1840. As a matter of fact and interest, the occurrence of duodenal ulcers after skin burns was noted by Cumin (1823), Dupuytren (1832) and Cooper (1840). Erichsen wrote a complete memoir on this subject in 1843.

Duodenal ulcers are not constant sequelae of burns and are admittedly uncommon, yet they occur with sufficient frequency to assure us that they are not merely coincidental. They are seldom diagnosed in the living, hence it is likely that many of these ulcers form and heal without the patient's or physician's knowledge. Necropsy reveals varying percentages, a fact that can be partially attributed to the time of death. If death takes place three or four weeks after the accident, ulceration is seldom found. Curling has observed that recently healed ulcers in the duodenum are occasionally found when death has occurred from other causes, some time after the burn. The age of the patient appears to be without influence on the incidence of occurrence. The ulcers are seen more frequently in women. In Erichsen's series of sixty-eight patients, two had duodenal ulcers. Ronchese saw them only once in 348 burned persons.[71] Holmes gave an illustration of their relative

68. Hall, J. N.: New York M. Rec., Aug. 15, 1896.

69. Schjerning and Seeliger, quoted by Silbermann: Centralbl. f. klin. Med., 1895, no. 20.

70. Curling, T. B.: Med.-Chir. Tr. London **25**:260, 1842.

71. Ronchese, F.: Riforma med. **40**:753 (Aug. 11) 1924.

frequency as in 125 cases of severe burns collected by him the duodenum was ulcerated in 16, and other portions of the intestines in 2 others. Of all fatal burns, 6.2 per cent are complicated by ulcer formation (Fenwick).

The causal relation of the burns to the ulcers is still held doubtful by some pathologists. Some say that the situation of the external injury exercises no influence, while others agree that it is more frequent after burns of the abdomen. The exact mechanism of formation of the ulcer is as yet unknown, but of theories there are plenty:

1. Curling believed that the duodenal glands of Brunner sympathized and compensated for the suppression of the exhalation from the skin by an increased activity. This, he theorized, leads to an irritation which causes inflammation and ulceration.

2. The antiferments of the mucous cells are reflexly destroyed (Cooke).

3. A reflex inhibition of intestinal circulation causes the ulcer.

4. An inhibition of gastro-intestinal circulation results from a depressed action of the heart or from impaired nourishment of the mucous mebrane (Falk).[72]

5. An inhibition in the force of the circulation results from accumulation of waste products in the blood (Leube).

6. The duodenal ulcer is due to the action of gastric juice or of intestinal and pancreatic enzymes on some part of the mucous membrane in which the circulation has been arrested by congestion or by embolism.

7. A toxin reaching the intestinal wall causes a reduction in its natural alkalinity, allowing digestion of the mucosa to ensue (Catiano).[55]

8. William Hunter was the original exponent of the theory that the duodenal ulcer was due to the irritant action of the noxious bile. The bile was assumed to owe its injurious ability to its content of the presumptive burn toxin, secreted by the liver. Dacosta gives, as antagonistic data, the evidence that the typical duodenal ulcer occurs well above the ampulla of Vater.[73]

9. Billroth was the first to define it as an embolic process. The infarcted area sloughs away.

10. Sir Berkeley Moynihan suggests septic emboli as the cause, because the ulcer never occurs unless the burn area is undergoing certain septic changes.

From these statements it can readily be seen that the consensus of opinion favors the theory that toxins are responsible for the formation of duodenal ulcers. Busse[74] attempted to reproduce these ulcers by injection of burnt skin extracts into laboratory animals. He failed to induce ulcer formation, but did cause hemorrhage and inflammation which, however, were not specifically limited to the duodenum, but involved also the stomach and jejunum.

The duodenal ulcer is usually single, but in exceptional instances may be multiple (five or six). Opinions vary concerning the common

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72. Falk: Virchows Arch. f. path. Anat. **4**:68.

73. Dacosta, J. C.: Modern Surgery, ed. 8, New York, W. B. Saunders Company, 1919.

74. Busse, O.: Verhandl. d. deutsch. path. Gesellsch. **17**:290, 1914.

location of the ulcer. Some pathologists believe that they generally occur in the upper transverse duodenum, near the pyloric end, seldom lower down (Kemp,[75] Sajou); others find them in the descending part of the duodenum close to the orifice of the bile duct. Curling says the ulceration takes place "in that particular part of the duodenum, where it passes in front of the head of the pancreas, rendering these cases very prone to the occurrence of hemorrhage, owing to the arteria pancreatica duodenalis running so close to the walls of the intestine in its passage between the duodenum and the pancreas as almost necessarily to become exposed when perforation ensues." [76]

The ulcers vary in size from that of a pinhead to that of a quarter. The amount of tissue loss may be considerable or slight, as in some instances the lesion is but a mere erosion whereas in others it is a rapidly sloughing perforative process. The shape of the ulcer is irregular and dentate or long and narrow, occasionally circular. The edges are sharply and cleanly cut, and the base is clean and grayish. The ulcers are practically always acute, but if they persist for any short period of time, the edge tends to become indurated. There may not be much inflammation surrounding the margin of the ulcer. It is frequently funnel-shaped, due to the loss of more mucous membrane than muscle tissue. When perforation is threatened, lymph and fibrinous exudation are frequently found on the peritoneal surface, a preformed and protective barrier to the lethal progress of the disease. The factor of time may exert some influence on the depth of penetration of the ulcer, but the age of the ulcer cannot be accurately estimated from this, since it is so insidious and asymptomatic in its incipiency as to elude diagnosis. Perforation has occurred as early as five days after the patient received the burn. Duodenal ulcers proceed to perforation, hemorrhage or spontaneous healing.

Curling implied that the duodenal localization of the ulcer was specific, but literature reveals many instances in which the stomach also was involved. Novak [77] reported a necropsy, which showed from forty to fifty small, punched-out lesions in the gastric mucosa, all within 3 inches of the pylorus. The duodenum was normal. One of Dupuytren's patients had many large and small gastric ulcers, but none in the duodenum. In most instances when gastric ulcers are found (and this is rare), the gastric ulcer is associated with duodenal ulcers.[78]

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75. Kemp, R. C.: Diseases of Stomach, Intestines and Pancreas, New York, W. B. Saunders Company, 1913, p. 683.

76. Quoted by Ashhurst, J.: International Encyclopedia of Surgery, 1881.

77. Novak, E.: Gastrointestinal Ulceration Following Cutaneous Burns, Am. J. M. Sc. **169**:119-125 (Jan.) 1925.

78. Stengel, A., in Osler: Modern Medicine, Philadelphia, Lea & Febiger, **5**, 1908.

Among the serious functional complications of burns and scalds are the cicatrices and contractural deformities which result from the healing of extensive burns.

BURNS FROM ELECTRICITY

The cause of these burns is usually an accidental contact of the body with a wire or other conductor of an electric current. It is the contact of the wire or electrode with the skin that causes the local damage.

There is no definite amount of electricity that the body can endure. Direct electric currents are much less dangerous, caeteris paribus, than the industrial alternating currents, but the more rapidly alternating the current, the more the patient is able to tolerate. Induced currents are also more destructive as a rule than direct currents. If the voltage is high and the amperage abundant, death can result with relatively insignificant local lesions. If the voltage is only moderate and the amperage remains large, severe and even fatal burns may be received.[79]. An alternating electric current of low amperage is not very harmful, even when the voltage is of fairly high tension. Currents of large quantity (amperage) are not necessarily dangerous to life if the voltage is low, although a burn can result if good contact is made. The degree of injury to the body is more or less proportional to a combination of some of the factors mentioned above and to the duration of the contact; for example, a milliamperage of 400 to 500 and the high voltage that is essential for its production and maintenance can produce a burn of great severity. The concentration of the current is also important, for with the same strength of current, the smaller the surface of the electrode in contact with the skin the more the lines of electric flux are concentrated in passing through the tissue immediately subjacent to the electrode.

The Resistance of the Tissues.—The point of entrance of the current is the anode or positive pole and the point of exit, the cathode or negative pole. The current loses in strength because of resisting forces opposing it. The strength of the current will increase with the electromotive force and will decrease with the resistance offered and vice versa. Ohm's law formulates this as:

Current strength (amperes) $= \frac{\text{E.M.F. (volts)}}{\text{Resistance (ohms)}}$. The resistance of the skin is less when moistened, especially over sweat gland ducts or hair follicles. The order of resistance of animal tissues is bone > fat > tendon > skin > muscle > blood > nerve.[80] The blood vessels are

79. Johnson, A. B.: Surgical Diagnosis, New York, D. Appleton & Company, **1**, 1910.

80. Pack, G. T.; Underhill, F. P.; Epstein, J., and Kugelmass, I. N.: Am. J. M. Sc. **167**:625-649 (May) 1924.

extremely good conductors of current, a fact that can no doubt account for the frequency of vascular lesions, such as the occurrence of thrombi. Electricity seldom causes burns of bone. Patel [81] reported the case of a patient who had a large electric burn over the left parietal area, with death of a bony segment. A dry or greasy skin is a poor conductor of electricity; consequently it presents a high degree of resistance to the entering current. The thicker the epidermis, the greater is the resistance. If the resistance of the skin is very low at the time it interrupts the electric circuit, the current passes readily into the body causing proportionately severe systemic disturbances, with little or no local damage at the point of entrance. However, if the skin maintains its high resistance, the current on coming in contact with it is temporarily halted, retarded and stored, the consequent friction generating a considerable quantity of heat, which burns the resistant tissue. "The greater the resistance, as long as the current passes, other things being equal, the more severe is the burn." [82] Hence we can understand why the burns occur at the regions of greatest resistance, especially at the points of entrance and exit of the current. The damage at the latter point is less severe than where the current enters the body. The foregoing facts explain the common occurrence of a burn of the sole of the foot while standing, because the electricity leaves the body at this place to enter the ground.

LOCAL CHANGES PRODUCED BY THE ELECTRIC CURRENT

The cellular changes induced by electricity are not well known. The electric current is more destructive to the nucleus than it is to the cytoplasm of the cell. H. Gideon Wells has suggested that the current causes an ionic migration toward the poles of the cells, thereby separating the movable inorganic ions of the ion-protein compounds from the immoble, unionizable colloidal proteins. This disruption of intracellular chemical associations seriously interferes with cell function.

The electric burn at first looks dry, crisp, bloodless and excavated. The contact of a weak current may be so light as only to singe the fine hairs on the skin. The severe burns, however, are usually deep, of various shapes and sizes, possessing clear-cut edges and surrounded by skin which appears whitened, bloodless and devitalized. Where a live wire has been in contact with the skin, there is a narrow and often blackened sulcus. Within thirty-six hours the skin around the eschar becomes hypersensitive, hyperemic and inflamed, with considerable oozing of serous fluid.[83] The eschar may become so edematous

81. Patel, M.: Lyon mèd., March 1, 1914.

82. Witthaus, R. A., and Becker, T. C.: Medical Jurisprudence, Forensic Medicine and Toxicology, New York, William Wood & Company, vol. 2.

83. Sharpe, N. W.: Philadelphia M. J., Jan. 29, 1898.

as to resemble moist gangrene or severe frostbite. Blister formation is not characteristic of electric burns, as here the tissues are cooked too thoroughly. The tissues at the point of contact may actually be destroyed down to the bone. The tissue beneath the superficial eschar often becomes inflamed, edematous and distended with gas formed by the necrosis, the whole producing a constant painful tension.[84] Occasionally the skin is apparently not damaged to any extent, as noted by the initial inspection, but after several days new cutaneous lesions develop and break down. There may be the same experience when an electric burn is clean and almost completely healed, as it then sometimes ulcerates and large masses of tissue slough away. This can be attributed to the peculiar abiotic action of electricity. Instead of killing the tissues outright, some are only fatally injured and require considerable time for death to occur. The underlying muscles, which are often paretic, may engage in the sloughing. There is a fluid state of the blood extending for some distance from the local lesion.[85]

The lesion resulting when the current leaves the body resembles a gunshot wound as the contiguous skin is scorched, and there are radiating tissue tears (MacCallum). When a high tension current passes in and out of a limb without traversing the general body cavity, we may expect severe burns out of all proportion to the mildness of the clinical symptoms. Macleod attributes the injuries of the skin to the electrolytic action of the electric current plus the intense heat generated by the resistance of the skin to the electric current.

The faradic current rarely causes a burn, except by a careless spark from a static machine. Small, circular, multiple, punched out, sharp edged, painless burns occur with the medical misuse of the galvanic current. These little burns, which heal quickly, are the result of imperfect or prolonged contact of the electrode with the skin.

The severity of the electric burn is at first generally underestimated, as it is extraordinarily persistent and hard to heal. It requires from one and a half to three times as long a time for recovery as ordinary burns. The resultant scar is thin, atrophic and variously colored (white, pink, red and pigmented). Scattered areas of telangiectasis are visible.[1]

Electric Burns of the Eye: When the visual organs have been injured by an electric spark or by contact with an electric current, the eyelids become red, swollen and edematous. There is a mild hyperemia and inflammation of the conjunctiva. The cornea may be superficially burned. The retina exhibits certain pathologic changes which Davier said was the result of an "electrocution" of the retina. The papilla and

84. Miller, S. R.: Internat. J. Surg. **34**:423-425 (Dec.) 1921.
85. Elder: Montreal M. J., January, 1900, p. 18.

large vessels are surrounded by areas of cloudiness which obscure the normal transparency of the retina. The borders of the papilla are not so definitely demarcated as usual. The blood vessels are diminished in size. It has been said that optic nerve atrophy is not the usual sequel to these changes.[86] Cataract has been reported as a not infrequent complication, resulting, some say, from the electrolytic action of the current, but it is probably secondary to an iridochoroiditis.

General Pathologic Anatomy.—There are no lesions of gross character found within the body that can be called pathognomonic for death by electricity. Postmortem examination, however, does reveal some constant findings. The heart musculature is flaccid and the right side of the heart is filled with dark fluid blood. Many of the viscera (liver, lung and kidney) are congested. There may be subpleural, cerebral and intrameningeal capillary hemorrhages. Chromolytic changes are indicative of nerve cell degeneration in the ganglion and cerebral cells. The general or visceral lesions are not so different from those of burns caused by other forms of heat.

Spitzka has stated that the body temperature may be elevated to 120 or 129.5 F. within twenty minutes after an electrocution; this temperature is sufficient to cause a heat coagulation of the myosin of the muscles.

The passage of the electric current through the body, especially a high voltage current, may be followed in a few days by gangrene of all of the extremities. This gangrene is due to endarteritic changes, which initiate thrombus formation.[87]

BURNS FROM LIGHTNING

"Lightning stroke is the passage of an aerial current of static electricity through the body." The effects of the lightning on the skin differs according to whether the stroke was directly or indirectly received and whether the mechanical or thermal action of the electricity predominates. Lightning can produce wounds of divers types and descriptions. There may be puncture wounds, lacerations, contusions, ecchymoses and simple or compound fractures of bones. Occasionally large blood vessels are ruptured, with dangerous hemorrhage. Instances have been reported in which an entire limb has been completely avulsed.

The burns may be of any degree and of any location. The face and shoulders are the most common areas of primary burning and are probably the points of entrance of the current into the body. Stripes and bands of burned or scorched skin may extend down the trunk and lower limbs to the point of exit or grounding of the current, where there

86. Oliver, Sir. T.: The Pathology and Treatment of Injuries Caused by Electricity, Lancet, Feb. 11, 1911, pp. 363-366.

87. Lucas, R. C.: Tr. Clin. Soc. London **38**:86, 1905.

is a secondary burning as in other electrical burns. Lightning burns are like other burns by electricity in that they seem to occur at the points of greatest resistance to the current flow, for example, at the points of entrance and exit of the current and where the clothes are tightly constricted about the body as at the neck, waist and knees. The effects of lightning and of the passage of the electric current are identical except for the peculiar pink or lilac colored arborescent skin markings found in the former. The cause and nature of this phenomenon are not known, but there are several theories:

1. The markings are due to the paralysis and dilatation of the superficial blood vessels (Jellinek).[88] Choyce and the majority of other writers believe that these skin markings do not follow the lines of the lymphatics or superficial blood vessels.

2. According to Rollet, they are visible because of the release of hemoglobin from the red blood corpuscles in the line of the lightning stroke, the persistence of the outline being due to the transudation of the coloring matter through the walls of the blood vessels.

3. Macleod explains these red lines as radiating from the sites of entrance and exit of the current, being formed "in the track of the discharge of the static electricity, which has been split up in a dendriform fashion, possibly through differences in the conductivity of the tissues."

4. The old discarded theory is that these arborescent skin markings were photographic imprints of trees, etc.

The eyes may be injured or destroyed. The mucous membrane of the nose and mouth has been burned. Death from lightning is rarely secondary to the burns incurred, but usually primary to the electric discharge. Consequently it can be said with some degree of certainty, that a person who survives the shock, stands an excellent chance of recovery.

BURNS FROM ROENTGEN RAYS

Marcuse was the first to note the tendency of these rays to burn the body.[89] The rays that pass through the tissues are practically without effect on them. Those that are absorbed by the tissues produce the well-known functional and pathologic changes. These tiny waves break up the atoms in their passage through it with the release of negatively charged ionic particles, which are responsible, in turn, for further damage. Burns are more readily caused by the softer and longer roentgen rays, because of their greater absorption and lesser penetration. The action of these rays is cumulative, so that a burn may be caused either by a single heavy overdose or by a series of individually harmless doses given at too close intervals.

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88. Jellinek, S.: Atlas der Elektropathologie, Vienna, 1912.
89. Marcuse, W.: Deutsche med. Wchnschr. **30**:481-482, 1896.

The surface intensity of the roentgen ray dose depends on four chief factors: the amount of filtration, the voltage, the target skin distance and the degree of sensibility of the individual affected. "The effect of the X-rays varies inversely with the square of the distance of the tube from the cutaneous surface" (Macleod). All persons do not exhibit an equal degree of tolerance. Fouts found a variation of 20 per cent in the tissue resistance and erythema dose of different persons. Moreover, he asserts, there are regional differences in susceptibility, e. g.: the pinnae of the ear, the skin over the sternum, the dorsum of the hand and the anterior surface of the leg will not tolerate a dose that other areas will with perfect safety.[90]

There are two schools of opinion concerning the mechanism of tissue degeneration: one maintains that the changes are wrought by the direct action of the rays per se;[91] the other attributes the localized necrosis and gangrene to ischemic phenomena produced by sclerosis of the blood vessels supplying the skin.

Classification of Roentgen-Ray Burns.—C. M. Sampson classifies these burns on a chronologic basis.

(*a*) Acute Burn: A localized lesion of varying degrees of severity from a simple erythema to an open ulcer with an erythematous margin, bordered by healthy skin. This results from one or more exceptionally heavy doses.

(*b*) Chronic Burn: A diffuse and multiform lesion identified by hyperkeratoses, skin atrophy and multiple small ulcers. This results from a series of frequently repeated doses over a prolonged period of time.

Fouts classifies acute burns by degrees.

First Degree: Simple erythema: It begins in from four to ten days after exposure and very quickly subsides. Epilation occurs within three weeks but is not permanent.

Second Degree: The erythema appears in from three to seven days and is of longer duration. The superficial epidermis desquamates in flaky layers and leaves a residual pigment in the skin.[92] The hair follicles are permanently destroyed.

Third Degree: The erythema is more intense and is accompanied by painful subjective sensations. Vesicles form on the edematous skin about two weeks after the exposure. Skin necrosis later appears. The slow healing lesion leaves a permanent hairless scar.

Fourth Degree: In addition to the changes found in the third degree there is an escharotic necrosis and extensive sloughing of the subcutaneous tissues, fasciae and muscles, leaving a deep, painful, slow-healing ulcer which is stubbornly resistant to treatment.

The Pathologic Histology of Roentgen-Ray Burns.—The histologic picture varies with the age and degree of the burn. The primary

90. Fouts, R. W.: J. Radiol. **5**:147 (May) 1924.
91. Ellis: Am. J. M. Sc. **125**:85, 1903.
92. Beck, C.: New York M. J. May, 1902, p. 24.

erythema is characterized microscopically by a dilatation of the cutaneous blood vessels with considerable transudation of serum and a resultant local edema. The capillary endothelium is turgescent and by its swelling partially obliterates the lumina. There is a perivascular infiltration of leukocytes, which also surround the edematous and injured hair follicles and sweat glands. It seems that the hair follicles, sweat glands, blood vessels and nails are more susceptible to the toxic influence of the roentgen rays than the less differentiated tissues of the skin.[93] The cells of the malpighian layer of the skin exhibit cloudy swelling and some of the intracellular features of simple necrosis, i. e., karyolysis, karyorrhexis and pyknosis. When healing is well established, this same malpighian layer has an increased pigment deposit. There are two theories to account for the presence of this extra pigment: (*a*) It is the direct result of melanoblastic stimulation by the rays. (*b*) It is a consequence of the dermal inflammation.[94] Healing is rapid and the tissues are restored to their normal condition.

If the burns are more severe, the tissue changes are correspondingly more extensive. The cell nuclei are injured so that the normal mitosis and cell multiplication are either stopped or abnormally stimulated. Some of the blood vessels are thrombosed; others are ruptured with small hemorrhagic areas pervading the tissue spaces. The thrombi become organized; a process of endarteritis obliterans begins, with a marked thickening of the intima and a breaking up or disappearance of the elastic lamina of the blood vessels.[95] The subendothelial layers are the seat of the greatest hypertrophy, the endothelium remaining intact throughout. Although not all the blood vessels are equally involved, the arteries are more seriously damaged than the veins. The corium shares with the epidermis in the paucity of blood vessels. Those blood vessels which persist in the corium are dilated and tortuous, but telangiectatic capillaries are newly formed in a perverted attempt to replace and substitute for the obliterated ones. The corium is dense and thickened by the formation of a hyaline, collagenous-like material.[96] This sclerosis of the corium is so great that the nuclei—which are abnormal in the quantity and position of their chromatin content—are few and far between. The whole of this area has poor staining qualities.[97] The sweat and sebaceous glands atrophy and disappear.

Obviously, changes of this character cannot develop except in lesions of long standing and possessing some degree of chronicity. The epi-

93. Macleod, J. M. H.: Brit. J. Dermat. **15**:365-374, 1903.

94. Freund, L.: Brit. M. J., October, 1902, p. 25.

95. Wyss: Beitr. z. klin. chir. (Bruns) **49**:185-216, 1906; Deutsche Ztschr. f. Chir., 1908, p. 93.

96 Cole, H. N.: J. A. M. A. **84**:865-874 (March 21) 1925.

97. Darier, J.: Ann. de dermat. et syph., October, 1912, pp. 541-562.

dermis having become necrotic and sloughed away, the surface of the ulcer is formed by a layer of granulation tissue, which is infiltrated with lymphocytes and plasma cells. New epithelium migrates over this granulation tissue from the margin of the ulcer, but the new epidermis formed is thin, sensitive to external influences and even in later years is likely to break down at the least provocation. The scarcity of blood vessels and the consequent lack of nourishment is partially responsible for the failure of repair and the slight tendency to heal. The epidermis in its search for nourishment or due to some abnormal growth stimulus, at times grows down into the corium in solid epidermal strands, which in certain instances exceed the normal growth proclivity and widely invade and permeate the tissues in the manner of a malignant tumor (Delafield and Prudden). The scar may undergo carcinomatous degeneration even years after the burning has occurred.

Gross Pathologic Anatomy of Roentgen-Ray Burns.—When the erythema fades, it leaves the skin discretely pigmented or freckled. If the irradiation is more intense, vesiculation and permanent epilation occurs, followed by skin atrophy. The burned skin may be tanned and parchment-like, remaining attached for a considerable period of time and thereby creating the erroneous impression that it will recover and not slough.[98] In the most severe degrees the sloughing may include the entire skin, the subcutaneous fat, the superficial fascia and even the muscles, although muscle tissue, by virtue of its better blood supply, has a better resistance. There is considerable secondary inflammatory reaction in the base and periphery of the injured areas, which is the vital response to the local cellular degeneration. The ulcers are slow in healing and have a fibrous scarred base which anchors the ulcer to the underlying tissue. This scarring is pernicious, and contraction occurs for months after healing is presumably complete, only finally to bring about a new ulceration.

In some of the chronic cases a dermatitis similar to xeroderma pigmentosum remains.[99] Roentgenologists have seen skin lesions of an erythematosquamous nature, followed by a skin atrophy in which the skin is dry, smooth, glistening and scaly.[100] Painful cracks or fissures may appear. The telangiectases previously mentioned may be visible as lilac colored tortuosities. Many pathologists have noted that these rays have a devitalizing effect on the nails, making them thin and brittle. The epidermis, while ordinarily thin, sometimes has scattered areas of hyperkeratoses, which are grayish white and verrucous. Because of

98. Blair, E. G.: J. Radiol. **5**:149 (May) 1924.

99. Stengel, A., and Fox, H.: A Text-Book of Pathology, New York, W. B. Saunders Company, 1921, pp. 27-32.

100. Stelwagon, H. W.: Treatise on Diseases of the Skin, New York, W. B. Saunders Company, 1910, pp. 425-430.

their location (usually on the hands), they are prone to trauma and infection. Such injuries may be influential in converting these precancerous areas into actual carcinomas. It has come to be an axiom that "a healed roentgen-ray burn is by no means a cured roentgen-ray burn." Since the recent advent of deep roentgen-ray therapy, tardy ulceration is not uncommon, and may appear from six weeks to two and a half years after the exposure.[101]

BURNS BY RADIUM

Radium produces acute and chronic burns that are almost similar in nature to roentgen-ray burns. The same classifications are applicable to both types of burns. The typical keratinization, corium induration, telangiectases, organized thrombi and precancerous tendency of the epithelium to grow downward that are seen in roentgen-ray burns are present also in burns from radium.[102]

The relative wave lengths and destructive power of the various rays of radium are as follows: alpha rays > beta rays > gamma rays. The penetrative ability of these rays is in inverse ratio to their wave lengths and destructive power. The hard beta rays and gamma rays do not ordinarily burn the tissues through which they pass, provided proper discretion and correct dosage are observed. The soft beta and alpha rays [103] are the most common causes of radium burn, as they are sometimes not sufficiently filtered out.

BURNS FROM THE SUN

The erythematous or erythematovesicular burn produced by the sun's rays or insolation is variously known as solar dermatitis, erythema solare and ephelis (the sun-Greek). More commonly it is called sunburn.

The human body is transparent and uninfluenced by all the waves of the great electromagnetic spectrum, with which it cannot vibrate in resonance. When the skin does vibrate in resonance with waves of the solar spectrum which fall on it and this vibration is not accompanied by friction, the particular waves in question are reflected, and thereby give the coloring to the features which is so apparent to the observer. But if these resonant vibrations are accompanied by friction, then the skin undergoes various thermal, chemical, physiologic and even pathologic changes, and the wave lengths responsible are said to be physiologically active. The substances composing the human body vibrate with the heat, light, roentgen and gamma rays; the physiologic action of these rays differs according to their own peculiar vibration frequencies, which

101. Rahm, H.: Beiträge zur klinischen Chirurgie, Tübingen **131**:456, 1924.
102. Wolbach: J. M. Res. **21**:415 (Oct.) 1909.
103 Rutherford, E.: Brit. M. J., Jan. 25, 1913.

in turn vary inversely with their wave length. In studying sunburn we are particularly concerned with the light waves of the solar spectrum, the various ones of which differ also in their physiologic effects, depending on their different vibration frequencies. In agreement with the fact that only those electromagnetic waves which are absorbed are effective in producing physiologic changes, the ultraviolet waves are the components of the complex solar rays which correspond most closely with the vibration frequency of the negative electrons of the tissues; hence they are absorbed quickly by the superficial skin. The red and infra-red rays have much longer wave lengths, penetrate much deeper into the tissues and are without demonstrable effect. Beyond the red rays of the solar spectrum are the still longer heat rays. It has long been known that the blue or violet end of the spectrum is the etiologic agent in sunburn; this would be expected, as it is known also that of the visible or optically active rays, the ones having the shorter wave lengths are photochemically the most active and intense. Talbot's law (quoted by Bovie [104]) formulates the factors influential in determining the degree of photochemical changes occurring in the skin: "The amount of chemical change produced by light is proportional to the product of the intensity of the light times the length of exposure, provided the vibration frequency is kept constant."

Finsen discovered that the blood in the skin absorbed the major portion of the sunlight ultraviolet so that deep injury cannot occur to well vascularized tissues. In the normal skin the ultraviolet waves penetrate only the short distance of 0.5 mm., but if the skin is rendered bloodless by pressure, these same rays will penetrate 4.25 mm. and produce inflammatory reaction at this depth. Fortunately, because of this fact sunburn is a superficial injury. The cornea of the eye is transparent to the ultraviolet rays, but they are mostly filtered out by the lens so that the inner eye is not usually directly damaged.

All persons are not equally susceptible to sunburn. Women and children, because of their delicate cutaneous covering, are burned more easily and severely. Blond and fair-skinned people are more sensitive to sunlight than brunettes. It seems that the melanin deposits in the skin are protective in nature by absorbing the ultraviolet rays, a theory that finds some degree of substantiation in the dark-skinned inhabitants of the tropics and in the extremely susceptible albinos. The phenomenon of tanning or increased melanin deposit in the skin seems to be an adaptive mechanism of the body in response to a heavy dose of sunlight. Some peculiarly constituted persons develop a hypersensitiveness of the nature of physical allergy to the sunlight, so that each succeeding sunburn is more easily acquired.

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104. Bovie, W. T.: Am. J. Trop. Dis. & Prev. Med. **2**:506-517, 1914-1915.

The exact mode of action of the ultraviolet light on the skin is unknown. MacCallum likens it to a catalytic agent which induces chemical decomposition and oxidation, especially of the lipoid substances. One pathologist believes the nature of the action on tissue proteins is coagulative, while another attributes it to the destruction of intracellular enzymes by the light. Still another claims that the light stimulates the oxidizing enzymes directly, and the necrotic changes are due to these oxidative changes. The blue rays of the electric arc light are only slightly cytotoxic, but Ogneff has demonstrated that the ultraviolet light from the same source causes mitotic cell division; if the action is stronger, the cells undergo amitotic division and finally become necrotic.[105]

The exposure of the skin to the sunlight leads to a mild irritative dermatitis which seldom progresses beyond the erythematous stage. It is practically a first degree burn of the exposed skin areas, usually the face and not infrequently the trunk and limbs of bathers. The skin is reddened, tense, swollen and edematous. In more severe cases after prolonged exposure, the excessive edema of the skin facilitates the formation of vesicles.

Histologically the skin presents a typical inflammatory reaction. The blood vessels are widened, as are the lymphatic spaces. There is a perivascular infiltration of mononuclear leukocytes. The fluid transudate permeates the corium and macerates and vacuolates the epidermis.

The conjunctivae may be inflamed and the eyelids almost swollen shut within forty-eight hours of the sunburn. When the skin over the joints is involved, the joints themselves may be swollen and stiff. The vesications may become infected and lead to scarring, which scars have pigmented margins. Sunburn of the lip (solar cheilitis) is painful and requires from ten to twelve days for recovery, because the thin epithelium of the labial mucous membrane is entirely destroyed and healing must occur by the growth of the marginal epithelium inward. In normal uncomplicated cases, after the subsidence of the inflammation, layers of the skin desquamate, leaving a residual pigmentation of various degrees.

If the exposure is prolonged or constant, as in middle-aged seamen and farmers, a chronic indurative condition of the skin results with hyperkeratotic, atrophic and ulcerative areas (chronic solar dematitis). At times the skin inflammation assumes the appearance of an eczema and is then known as eczema solare. Mild sunburns subside in from thirty-six to seventy-two hours.

BURNS FROM CAUSTIC CHEMICALS

A typical lesion produced by chemical caustics presents a pathologic picture showing all the progressive stages and degrees of destruction

105. Ogneff: Arch. f. d. ges. Physiol. **63**:209, 1896.

from a central chemical solution and the deeper area of cell death and necrosis to the peripheral and basal layer, exhibiting a hypermic inflammatory reaction.[106]

The principal caustic alkalis of medical interest are sodium hydroxide, potassium hydroxide and lime. They exert their pathologic action by three different means; they saponify the fats; because of their hygroscopic nature, they abstract considerable water from the cells; they unite with the proteins of the tissues to form alkaline albuminates. The epidermis is rendered swollen and translucent, separating as a dead necrotic layer from the underlying red and inflamed corium. The alkalis are capable of deep penetration and are productive of severe pain.

The concentrated acids, particularly the mineral acids, have somewhat similar actions: they withdraw water from the cells; they facilitate the solution of epithelium and connective tissue; they are protein precipitants, forming acid albuminates and hydrolytic acid metaproteins.[106] Sulphuric acid converts the corroded tissues into a greenish black or dark brown slough, the color of which is due partly to the formation of acid hematin and partly to the carbonization of the eschar, brought about by the splitting off of the elements of hydrogen and oxygen from the protein and carbohydrate molecules to form water with which to quench the thirst of the sulphuric acid. Hydrochloric acid stains the skin brownish yellow;[107] nitric acid leaves a yellow color, changing later to a yellowish brown (xanthoproteic reaction).

The corrosive action of the organic acids is proportional in some degree to their volatility. The volatility of these acids seems to determine the extent of their penetration into the tissues. Trichloracetic acid, therapeutically used as a caustic, is the most corrosive of all the organic acids. It forms a white soft slough. Phenol is a destructive and poisonous organic acid, causing an initial white slough that later turns greenish black or copper color. Chromic acid stains a greenish brown and tends to cause chronic ulceration of the skin and nose. Oxalic acid is more toxic than caustic. The intensity of the corrosion produced by these acids is proportional to their concentration.

White phosphorus burns of the surface are deep injuries, because the phosphorus burns until it is entirely consumed. The lesion differs from those of other caustics because of the occasional presence of vesicles or bullae. Phosphorus adheres to the flesh, where it continues to fume and occasionally splutters into little bursts of flame.[108] Zinc and tin chlorides are acid salts which are capable of burning the skin.

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106. Sollmann, T.: A Manual of Pharmacology, New York, W. B. Saunders Company, 1918, pp. 115-125.

107. Chambert: Ann. d'hyg. **11**:342, 379, 1859.

108. Walton, D. C.: J. A. M. A. **84**:1569-1570 (May 23) 1925.

Bromine is the most corrosive of the halides because of its heaviness, volatility and power of penetration. Bromine stains the skin an orange or light brown. Silver nitrate (lunar caustic) produces a superficial black eschar.

Caustic Burns of the Alimentary Tract.—Alkali and acid burns of the tongue are deeper and more painful than scalds of the same organ. The posterior part of the tongue suffers more than the anterior part; in some instances the tongue may escape almost completely, the esophagus and stomach receiving the greatest injury. The tongue swells until it approaches the size of the macroglossia of parenchymatous glossitis. The mucous membrane peels off as a dead, necrotic layer, leaving a reddened, exquisitely tender surface.

In accidental cases, the injuries are usually limited to the mouth, fauces, pharynx and larynx. The volatile or fuming liquids, as ammonia, bromine, chlorine and nitric, nitrous, hydrochloric, sulphurous, acetic and formic acids, act rapidly and penetrate deeply. Their fumes may be inhaled and irritate the mucous membrane of the respiratory tract, causing coryza, edema glottidis, bronchitis and pneumonia.

In suicidal cases, the soft palate, fauces, esophagus and stomach are usually affected, in addition to the oral lesions. The corrosions are greater in those areas in which there is prolonged contact of caustic and tissue, i. e., the lips, pharynx, pharyngeal and cardiac orifices of the esophagus, constricted portions of the gullet as where it traverses the left bronchus, etc. The esophagus may be congested and inflamed throughout its whole extent.

Phenol, mercuric chloride and some other substances corrode the stomach, but have in addition such prompt poisonous action that they demand especial consideration. The heavy mineral acids and the caustic alkalis so injure the stomach that surgical intervention is sometimes necessary. The concentration of the substance swallowed is of greater prognostic importance than the quantity. The stomach violently contracts the moment the irritant caustic comes in contact with it, and by this contraction forms a trough along the lesser curvature, thereby protecting the greater portion of the gastric mucosa. The caustic, if liquid, flows along this trough and accumulates at the pylorus, consequently it is these portions that are most severely burned. The firm spasmodic closure of the pylorus protects the intestines, but in rare instances some of the caustic passes the pylorus and burns the duodenum. When the quantity of acid or alkali swallowed is very great, the entire surface of the gastric mucosa may be damaged. The character of the lesion depends on the nature of the caustic, its concentration, duration of contact and the size of surface involvement. The lining membrane may be only slightly hyperemic, as in acute catarrhal gastritis, or it may be

blackened, disintegrated and sloughing off in large shreds or patches. If the patient survives the immediate shock, a hemorrhagic inflammation of the stomach wall ensues. The corrosion has been so deep as to perforate the stomach and permit the caustic to burn other viscera, as the liver, spleen and pancreas.[109] A local or generalized peritonitis follows rupture of the stomach.

Caustic Burns of the Eyes.—Acid burns of the eyes are painful because of the great sensitiveness of these organs. The most common agent is phenol, which is superficially destructive, but may be followed by leukoma. The after-effects of these burns are likely to be progressive and cause damage to the interior of the eyeball, as cataract, iritis, etc.

Ammonia fumes are irritant to the conjunctiva. If their contact is prolonged, an actual destruction of tissues occurs; but as a rule, the eschar is superficial. The lesion is exquisitely painful.

The great majority of alkaline caustic burns of the eye are caused by lime, usually partially slaked lime, mortar or plaster. When a particle of lime enters the eye it sets up a violent irritation which induces a copious flow of tears and a spasmodic closure of the eyelids. This is disadvantageous, because the lime is held in close apposition with the eyeball, and the tears permit the hydration or slaking of the unslaked lime with the evolution of great heat, thereby increasing the caustic action. Hence the tears aid and abet the burns by lime, although they are safeguards against acid burns because of their diluting action. Lime forms a chemical combination with the cornea to produce an opacification composed of calcium albuminate and predominantly calcium carbonate. The latter is responsible for the major portion of the opacity and probably increases in quantity with time, owing to the conversion of the unstable calcium albuminate to calcium carbonate by the union with the carbon dioxide of the tears and atmosphere.[110]

SUMMARY

Various etiologic agents may be responsible for causing burns and scalds: dry heat, moist heat of various kinds, the actual flame, heated solid bodies, electricity, roentgen rays, radium, sunlight and caustic chemicals.

Thermal traumas are best classified in six degrees to denote the various depths of tissue invaded or destroyed. The local tissue changes progress through the various stages of destruction or burning, inflammation and sloughing and finally regeneration and repair. The amount

109. Bergmann, E. von; Bruns, P. von, and Mikulicz, J. von: A System of Surgery, trans. by W. T. Bull, New York, Lea Bros. & Co., **4**, 1904.

110. Barkan, O., and Barkan, H.: J. A. M. A. **83**:1567 (Nov. 15) 1924.

of local tissue destruction varies from simple erythema and the degrees of vesication to an involvement of the entire epidermis, dermis, subcutaneous tissues and even muscle and bone, when there is great intensity or prolonged contact of the heat. Scarring is inevitable when the papillary layer of the skin is destroyed.

The liver, brain, bone marrow and kidneys of the burned patient may exhibit hyperemia, focal necroses and parenchymatous degenerative lesions. The suprarenal glands are swollen and deep red owing to hyperemia and ecchymotic areas of hemorrhage among the parenchymal cells. The spleen, the lymph glands and the solitary and agminated lymph nodules of the intestinal tract are the seats of toxic focal necroses occurring in the centers of the germinal follicles. This necrosis is quickly followed by the rapid proliferation of endothelial leukocytes.

The erythrocytes undergo certain alterations in structure and disturbances of function. Leukopoiesis is stimulated by the burn toxin, so that leukocytosis occurs with an increased percentage of neutrophilic polymorphonuclears. A predisposition to thrombosis exists because of the leukocytic disintegration, the venous stasis and the viscidity of the concentrated blood. A goodly portion of the visceral pathology has been attributed to the presence of minute capillary thrombi. The rapid and continuous loss of fluid from the blood in burned patients quickly induces a marked concentration of the blood. This becomes a factor of the greatest importance in the development of the syndrome characteristic of burns, and a factor of prime significance in the fate of the person concerned. Changes observable in the chemical composition of the blood during burns vary at most only slightly from the normal limits.

The urine is subjected to certain quantitative and qualitative alterations, such as oliguria, albuminuria, albumosuria and acetonuria.

The hypothetic burn toxin has its source of origin in the burned tissues, from whence it is absorbed and circulates in the blood, being carried by the red blood corpuscles. The exact nature of the burn toxin is as yet unknown, but it is probably closely related to the primary and secondary proteoses or to other products of protein disintegration.

The most common complication of burns and scalds is a secondary pyogenic infection of the burned area. Other complications which occasionally occur are: nephritis, septicemia, tetanus, wound hemorrhage, meningitis, apoplexy, pneumonia, amyloid infiltration of the viscera and cicatricial contractural deformities. The inconstant duodenal ulcer of burns is due either to the irritant action of the bile, which owes its injurious ability to its content of the presumptive burn toxin, or to the production of infarction of the duodenal mucosa by septic emboli.

Electric burns occur at the areas of greatest resistance to the current, particularly at the points of entrance and exit. The electric burn is

characterized by extensive sloughing of tissue, delayed healing and the absence of vesicles. The type of lesion produced by lightning varies according to whether the mechanical or thermal action of the electricity predominates. Lightning burns are further characterized by the occurrence of peculiar pink or lilac colored arborescent skin markings.

The tissue degeneration caused by the roentgen rays and radium is due to one or both of two mechanisms; either the changes are wrought by the direct action of the rays per se, or the localized necrosis and gangrene is the result of ischemic phenomena produced by sclerosis of the blood vessels supplying the skin. These burns are slow to appear, slower to heal and have a decided tendency to undergo malignant degeneration.

Sunburn is an erythematous or erythematovesicular burn produced by the action on the skin of the ultraviolet components of the complex solar rays.

Chemical caustics produce a lesion which exhibits a central solution, a deeper layer of cell death and necrosis and a peripheral layer in which the inflammatory reaction appears. Caustic alkalis penetrate deeply and bring about their pathologic action by three different means: they saponify fats; they withdraw water from the cells; they form alkaline albuminates. The concentrated mineral acids likewise withdraw water from the cells; they dissolve epithelium and connective tissue; they form acid albumonates and acid metaproteins. The corrosive action of the organic acids is proportional to their volatility. The character of the burns of the alimentary tract depends on the nature of the caustic, its concentration, the amount swallowed, the duration of contact and the size of surface involvement. Caustic burns of the eyes are exquisitely painful and are often followed by visual impairment secondary to iridochoroiditis, corneal opacification, etc.

Notes and News

Investigation of Otosclerosis.—The Carnegie Corporation of New York has appropriated $90,000 to the American Otological Society for an investigation of otosclerosis during the next five years.

Malta Fever.—In discussing the results of treatment of malta fever, Domingo (*Rev. Méd. de Barcelona* **4**:240, 1925) states that in the course of four years four of his laboratory assistants contracted the disease.

Society for Experimental Pathology Elects Officers.—The Society for Experimental Pathology has elected W. H. Brown president, David Marine vice-president, and G. B. Krumbhaar Secretary, for 1926.

Paris Appointments.—In the faculty of medicine of Paris, Dr. Francis Rathery has been elected professor of experimental pathology and Dr. A. Lemierre, professor of bacteriology.

Prize Awarded Professor Zangger.—The prize of the Marcel Benoist endowment, Zurich, has been awarded this year to Professor H. Zangger, director of the medicolegal institute, Zurich, for his recently published work "Vergiftungen."

Banti Prize for Researches in Pathologic Anatomy.—The University of Florence has received from Argentina 50,000 liras collected by Professor Dessy. The interest is to be used as the Guido Banti prize for researches in pathologic anatomy.

Pathologist Appointed Health Commissioner.—Dr. Herman G. Weiskotten, acting dean and professor of pathology at Syracuse University College of Medicine, has been appointed commissioner of health of Syracuse to succeed Dr. Thomas P. Farmer, who resigned to devote his time to private practice.

Dr. Kirkwood Accepts New Appointment.—Dr. R. C. Kirkwood, during the World War chief of medical service at the Army General Hospital, Ft. Bayard, N. M., more recently attached to the Army Medical Research Board in the Philippines, has recently resigned from the medical corps of the army and accepted appointment as epidemiologist, State Board of Health, Salt Lake City, Utah.

The Trudeau Medal of the National Tuberculosis Association.—This medal is to be awarded in accordance with the following resolution:

"*Resolved,* That the Board of Directors hereby approves the plan of the Committee on Medical Research for the awarding of a gold medal not oftener than once a year to that individual who, in the judgment of the Association, has made the most meritorious contribution on the cause, prevention or treatment of tuberculosis during the previous year; the medal to be known as the Trudeau medal of the National Tuberculosis Association and when awarded the name of the recipient to be announced at the annual meeting of the Association."

The medal was designed by Mr. Theodore Spicer-Simon and shows an excellent likeness of Dr. Trudeau in bold relief; on the reverse side is symbolized the tree of knowledge, the use of test tubes and animals in experimental work on tuberculosis.

Society of American Bacteriologists Elects Officers.—The Society of American Bacteriologists has elected officers for 1926 as follows: president, Hans Zinsser, Harvard Medical School; vice-president, Robert S. Breed,

The name of the first recipient of the medal will probably be announced at the annual meeting in October, 1926.

Fig. 1.—The Trudeau medal of the National Tuberculosis Association.

Fig. 2.—Reverse side.

Agricultural Experiment Station, New York; secretary-treasurer, James M. Sherman, Cornell University; councilors: S. Henry Ayers, C. C. Bass, F. M. Huntoon, and Karl F. Meyer.

The Carlo Forlanini Foundation.—This foundation, established in the name of the famous clinician (1847-1918) of Pavia, who, it is said, was the first—1895—to employ pneumothorax in the treatment of pulmonary tuberculosis, has announced a prize of 10,000 liras to be awarded to the best work submitted dealing with the pathologic anatomy, the pathogenesis or the treatment of pulmonary tuberculosis. The original work must be presented to the Direzione dell'Ospedale Maggiore in Milan, Italy, by Dec. 31, 1926.

Sedgwick Memorial Lectureship and Medal Funds.—In recognition and perpetuation of the services and ideals of Professor W. T. Sedgwick, pioneer in public health work, it is proposed to establish by permanent endowment a Sedgwick Memorial Lectureship and a Sedgwick Memorial Medal. The medal will be awarded by the American Public Health Association for distinguished service in the cause of public health. The lectures will be on biology or public health. Three lectures have been given. Additional funds are needed for both these projects, and subscriptions may be sent to C. E. Turner or H. N. Calver, 370 Seventh Avenue, New York.

Navy Adopts Kahn Test as Standard.—The U. S. Navy Medical Department, Dec. 30, 1925, notified all medical officers that hereafter the Kahn test would be regarded as the standard test in the serum diagnosis of syphilis and yaws, and that it be so employed as a routine. It is now purely optional whether other tests are employed in the navy, but if employed, they are to be in addition to the Kahn test. Unit outfits containing the necessary apparatus will be furnished all ships and stations on requisition to the U. S. Naval Medical Supply Depot, Brooklyn, and standardized antigen can be procured on request from the commanding officer, U. S. Naval Medical School, Washington, D. C.

Joint Study of Expert Testimony.—The Cleveland Bar Association and the Academy of Medicine of Cleveland are conducting a study of problems involved in medical expert testimony. The committee will study these questions: (1) What has been done in other states in the past? (2) If an impartial group of medical expert witnesses could be used, should this group be established by the court or by the medical profession through its organizations? (3) What would be the effect of such a group on procedure in trial cases? (4) How should such a group be compensated for their services? and (5) What questions of constitutionality would be involved in any proposed change?

Registry of Tumors of Lymphatic System.—A registry of lymphatic tumors has been started by the American Association of Pathology and Bacteriology. The same general plan will be followed as in the case of the registry of bone sarcoma by the American College of Surgeons under the direction of Dr. E. A. Codman. Suitable material with the essential data should be sent to the Curator, Army Medical Museum, who will be glad to supply necessary information to prospective contributors to the registry. The committee in charge consists of Dr. James Ewing and Dr. F. B. Mallory.

Fatal Necropsy Infections.—It is reported that Dr. M. B. R. Swan, demonstrator of pathology in Cambridge University, England, has died from septicemia contracted in the course of a necropsy. Last January, Miss C. Iris Fox, senior assistant pathologist at the Royal Free Hospital, died in the same way.

Abstracts from Current Literature

Pathologic Physiology

COMPENSATORY HYPERTROPHY OF THE THYMUS GLAND IN THE RAT. J. MARMORSTON-GOTTESMAN and HENRY L. JAFFE, J. Exper. Med. **42**:413, 1925.

Previous experimental work concerning enlargement of the thymus has dealt mainly with the regeneration which follows partial or subtotal removal, or with the regeneration which follows transplantation. The experiments of the authors were planned to obtain evidence of uncomplicated hypertrophy by removing one lobe and studying the enlargement of the remaining lobe. The results clearly indicate that such hypertrophy takes place in young animals. They emphasize the functional importance of this gland before puberty. The results further indicate that with the onset of involution there is a marked or almost total decline in the function of the gland, in spite of the fact that anatomically the thymus may persist to old age. With the appearance of a stimulus for regeneration, as, for instance, suprarenalectomy, the involuted gland takes on functional activity.

THE RESISTANCE OF FOWL TO STRYCHNINE. W. J. R. HEINEKAMP, J. Lab. & Clin. Med. **11**:209, 1925.

Fowls possess a relative immunity to strychnine only when the drug is given by mouth. The minimum lethal dose depends on the contents of the crop, the rate of absorption being inversely proportional to the amount of food in the crop and directly proportional to its fluidity.

Glucose, presumably by increasing the glycogen content of the liver, enables the animal to withstand a larger dose. This is not understood, but it may be due directly to the glycogen or its elaboration of a neutralizing agent.

S. A. LEVINSON.

TETANY AS A CAUSE OF CONVULSIONS IN WHOOPING COUGH. G. F. POWERS, Am. J. Dis. Child. **30**:632 (Nov.) 1925.

The convulsions in whooping cough may result from tetany; the only means of recognizing this is electric hyperirritability of the nerves, and a reduced concentration of calcium in the blood. The recognition of tetany is important in order that proper preventive and curative methods may be used.

STUDIES IN CARBOHYDRATE METABOLISM. III. INVESTIGATIONS INTO THE NATURE OF THE GLUCOSE IN THE BLOOD OF NORMAL INDIVIDUALS. C. LUNDSGAARD and S. A. HOLBØLL, J. Biol. Chem. **65**:323, 1925.

IV. INVESTIGATIONS INTO THE NATURE OF THE GLUCOSE IN THE BLOOD OF PATIENTS WITH DIABETES MELLITUS AND OF PATIENTS WITH BENIGN GLUCOSURIA. Ibid., p. 343.

V. Investigations Into the Form of Glucose in Different Body Fluids. Ibid., p. 363.

A method is described for determining the specific rotatory power of glucose in blood. The glucose in blood dialysate has a lower specific rotatory power than alpha and beta glucose. The mutarotation in the reversion of this substance to alpha and beta glucose corresponds with that previously noted for "new-glucose." "New-glucose" can be detected in the blood of normal persons both while fasting and after taking glucose. It is probably the first product of glucose transformation in normal carbohydrate metabolism.

New glucose is found in the blood of persons with benign glycosuria. It is seldom found in the blood of persons with moderately severe diabetes mellitus, and when found, it is removed from the blood stream in its passage through the capillaries. Insulin exerts its action in conjunction with a substance present in the muscles by transforming alpha and beta glucose into new-glucose which can then be further broken down by the tissues.

New-glucose is found in the spinal and pleural fluids and the fluid with edematous tissue of persons with normal carbohydrate metabolism. It is in greater concentration in spinal and edema fluids than in the dialysate from blood. This may be due to the fact that mutarotation of the new-glucose in blood has already begun during the necessary process of dialysis. This possible error is avoided in the examination of the clear tissue fluids.

Arthur Locke.

The Neurological Mechanism of Angina Pectoris and Its Relation to Surgical Therapy. Wilder Penfield, Am. J. Med. Sc. **170**:864, 1925.

The removal of a sympathetic ganglion removes the possibility of angina pectoris in the motor distribution of that ganglion only.

Pain is still possible in the motor distribution of the remaining ganglions, provided the stimulus arising in the heart or aorta is adequate.

Success in the operation depends not on interrupting a direct afferent path from the cardiac plexus to the central nervous system as has beeen assumed, but on the interruption of autonomic reflexes.

Complete cervico-upper-thoracic sympathectomy abolished the pain, but should only be employed in cases in which life is insupportable even under the best medical care.

Removal of the superior cervical sympathetic ganglion does not render angina in the motor distribution of the other ganglions impossible. Its removal can be justified only on the basis of some resultant alteration in the coronary vessels or aorta which are innervated by it through the superior cardiac nerve.

Even if the operation is successful in abolishing pain, the patient should not be called cured but should be considered as having a serious cardiac disease, and be treated accordingly.

Author's Summary.

(Left) Shoulder Pain of Phrenic Origin — A Reflex Symptom in Chronic Appendicitis. Irving Gray, Am. J. Med. Sc. **170**:894, 1925.

Three cases are reported in which pain in the left shoulder was associated with chronic appendicitis, acting reflexly through the phrenic nerve, and disappearing following appendectomy. The method of production of the pain is discussed.

THE EFFECT OF LIGHT ON THE CIRCULATION. D. T. HARRIS, Proc. Roy. Soc. Med. **99**:28, 1925.

Irradiation of a localized region of skin with ultraviolet energy causes a widespread peripheral vasodilation. Consequently, only a slight transitory rise of blood pressure results from the small increase in pulse rate. The response is enhanced by a previous exposure and appears to be a nervous reflex, initiated by a nocuous stimulus. The whole phenomenon is one of incipient injury.

ARTHUR LOCKE.

THE MECHANISM OF MUSCULAR CONTRACTION. W. E. GARNER, Proc. Roy. Soc. Med. **99**:40, 1925.

The tension generated on applying a stimulus to a muscle fiber is due to the formation of a solid film on the surfaces of the ultimate fibrils of the muscle. The manner in which a solid film may be produced on the surface of anisotropic segments by the action of lactic acid, and the conditions under which a tension can be developed, are discussed. The conclusions are in accord with experimental results on the force exerted and the total energy liberated by a muscle when stimulated under various mechanical conditions.

ARTHUR LOCKE.

THE EFFECTS OF CALCIUM AND POTASSIUM IONS ON URINE SECRETION, AS STUDIED IN THE WHOLE ANIMAL. L. BRULL AND F. EICHHOLTZ, Proc. Roy. Soc. Med. **99**:57, 1925.

Intravenous injection of potassium chloride into normal anesthetized dogs increases the urine flow much more than injections of corresponding amounts of sodium chloride. The increased flow is not due to hydremia nor to changes in blood pressure. Neither potassium chloride, calcium chloride nor their combination have any constant or specific effect on chloride output unless the pituitary body is first removed. (The kidney loses its power of concentrating chlorides after extirpation of the pituitary body.)

ARTHUR LOCKE.

THE ALTERATIONS IN CARDIAC FUNCTION IN INFECTIONS IN GENERAL AND IN DIPHTHERIA IN PARTICULAR. S. LA FRANCA, Arch. di pat. e clin. med. **4**:257, 1925.

The behavior of the heart during acute infections depends on several factors: the temperature, the toxins, anatomic lesions and extracardiac influences. The influence of temperature on heart rate is expressed by van't Hoff's law: the speed of vital functions is doubled or tripled for a 10 degree rise in temperature. The effect of toxins varies. The heart rate may be increased as in tuberculosis or decreased as in the typhoid type of fevers. Anatomic changes may precede the infection, the result of previous injury, old age or alcoholism, or may themselves result from the infectious process. The latter changes consist in degenerative and inflammatory lesions in the endocardium, myocardium or vessels. Extracardiac factors influencing the heart action are lesions of the lungs, kidneys or nervous system.

Disturbances of the heart in diphtheria are of various types: disturbances of contractility leading to cardiac weakness, of tonus permitting dilatation, of irritability causing extrasystoles and other abnormal rhythms, or of conductivity leading to heart block. The disturbances may appear early or during

convalescence. The severe types are rare, but milder types of irregularity during convalescence, sinus arrhythmia, extrasystoles, etc., are more common. Postmortem changes consist of the various types of myocardial degeneration.

B. R. Lovett.

Sino-Auricular and Auriculo-Ventricular Dissociation. A. Fulchiero, Arch. di pat. e clin. med. **4**:270, 1925.

The author discusses the question of cardiac block. He shows the incomplete identity of Morgagni's syndrome and defects in conductivity. In considering auriculoventricular block, he speaks of the different degrees of block, and of the simultaneous existence of block and fibrillation or auricular tachysystole. He considers the nervous influence on the autonomic rhythm, and the value in diagnosis of the pulse rate. The pathogenesis of block is fully considered, with some remarks on the prognosis and treatment. Eight cases are cited, with varying degrees of heart block, some with a simultaneous auricular fibrillation. The author concludes that auriculoventricular block occurs more frequently than usually believed, that nervous manifestations are often lacking, that they are present in some cases of paroxysmal block and usually disappear when the block has become permanent. He thinks that syphilis is not the etiologic factor in most cases, as it was present in only two of his eight.

B. R. Lovett.

The Action of Calcium in Reducing Inflammation. E. Lehner, Klin. Wchnschr. **4**:2106, 1925.

The inflammation-reducing action of calcium is confined to the locality in which the intracutaneous injection or iontophoresis is made.

Arthur Locke.

Blood and Iron Metabolism. L. Asher, Med. Klin. **21**:1909, 1926.

Splenectomy is followed by increased elimination of iron, which in dogs is normally about 16 mg. per day (15 mg. of it by the feces). Therefore administration of iron or food containing it is necessary to avoid anemia after splenectomy, although the spleen inhibits the hemopoiesis. Loewy discovered in the blood of animals subjected to low air pressure substances which stimulate regeneration of the blood (hemopoietins) Such serums are without any effect in rabbits after extirpation of the thyroid and thymus. In a similar way, injections of sodium nucleinate do not induce leukocytosis in such animals. If splenectomy is added, the reaction reappears, but the animals die—probably because they are unable to stand the losses of blood required in conducting the research when three of the regulating organs are removed.

Contribution to the Clinical Picture of Perirenal Apoplexy. J. Baló, Beitr. z. path. Anat. u. z. allg. Pathol. **73**:598, 1925.

Baló applies the term perirenal apoplexy to perirenal hemorrhage, which is usually sudden in onset. The hemorrhage may come from the kidney itself, from its capsules, or from rupture of nearby diseased blood vessels. It leads to sudden pain in the lumbar region through peritoneal irritation and may be associated with palpable swelling. The condition may run an acute or a chronic course.

O. T. Schultz.

THE MECHANISM OF INSULIN ACTION. E. F. MÜLLER, H. J. WIENER and R. v. E. WIENER, München. med. Wchnschr. **72**:1677, 1925.

The action is on the vegetative nervous system, promoting glycogen formation in the liver as well as the known blood sugar changes.

ARTHUR LOCKE.

EXPERIMENTAL STUDIES ON THE INTERNAL SECRETION OF THE TESTIS. S. FUJITA, Sc. Rep. Govt. Inst. Infect. Dis., Tokio **3**:85, 1924.

As a result of experimental ligation of the vas deferens and castration in rats, cats and monkeys, the author found: (1) no evidence for the theory of endocrine activity on the part of the interstitial cells; (2) the principal source of internal secretion in the testis is to be found in the germinating cells. Absolute nonparticipation of the interstitial cells could not be proved. (3) The interstitial cells appear to function principally as metabolic agents for the parenchymatus tissue.

H. E. EGGERS.

Pathologic Anatomy

THE PATHOLOGY OF PEPTIC ULCER OF THE STOMACH. HOWARD T. KARSNER, J. A. M. A. **85**:1376, 1925.

From his review the author concludes that the origin and persistence of peptic ulcer remain unsolved problems. The nature of the lesion has been clarified by the study of fresh material removed by operation. The inaccessibility of the field, the abnormalities produced by rendering it accessible, the complexity of nervous and vascular supply, the unsettled state of knowledge concerning the secretory and motor functions of the organ, the difficulty of establishing a norm of form and function, the differences between lower animals and man — these and other factors have led to the pitfalls in investigating the condition. The painstaking care and indefatigable energy of the numerous investigators of the disease have, however, thrown important light on the subject and have prepared the way for further and more fruitful investigations. Pathologically peptic ulcer is an inflammatory lesion so situated that gastric juice probably emphasizes the destruction of tissue. That the inflammation is primary is suggested but not proved. Various predisposing causes seem to be operative, but these are not conclusively established. The direct exciting cause of the ulcer has not yet been disclosed in such a fashion as to be beyond doubt. The persistence of chronicity of the ulcer depends on a variety of factors, none of which can be said to operate in all cases. Probably several of these factors are coincidentally in evidence. Thus, there must be considered especially hyperacidity stasis of neuromuscular or obstructive origin, the irritative and traumatic influence of gastric contents, and the traction of muscle about the ulcer.

INTRANUCLEAR INCLUSIONS IN VISCERAL DISEASE. WILLIAM C. VON GLAHN and ALVIN M. PAPPENHEIMER, Am. J. Path. **1**:445, 1925.

The anatomic diagnosis was abscess of the liver, ulcerative colitis, right suppurative pleuritis and organizing lobular pneumonia Intranuclear bodies were found in the intestine, liver and lungs, principally in cells in granulation tissue. The inclusions were like the bodies found in herpes and related conditions. In favor of the view that they represented a virus, it is pointed out

that they occurred in numbers only at the site of the lesions, that viruses of the type in question can cause inflammation, and that no other agent was discovered as the cause of the changes.

PROGRESSIVE ALCOHOLIC CIRRHOSIS. ERNEST M. HALL and W. OPHÜLS, Am. J. Path. **1**:477, 1925.

Inflammatory changes are present early in the connective tissue and at the same time evidence of injury to the liver cells is demonstrable, the two processes probably being due to a common cause The hyaline degeneration of the cytoplasm of the liver cells, noted by Mallory as peculiar to alcoholic cirrhosis, was present in the four cases studied by Hall and Ophüls.

L. HEKTOEN.

CASE OF TORTUOSITY OF INTERNAL CAROTID ARTERY. A. R. CADARSO and J. J. B. GOYANES, J. Anat. **110**:119, 1925.

The left internal carotid artery, 1 cm. below the inferior opening of the carotid canal, was disposed in a complete coil in the sagittal plane and was comparable in appearance with the coiled part of a manometer tube.

CYSTS OF THE PANCREAS. G. L. MCWHORTER, Arch. Surg. **11**:619, 1925.

The most frequent cause of retention cysts is chronic pancreatitis, which produces a gradual stenosis of the ducts and may give rise to single or multiple cysts. Obstruction of the pancreatic duct often causes cyst formation, but these cysts also are usually associated with pancreatitis. Dermoids and teratomas occur also. Pancreatitic cysts found in early life are due to proliferation of embryonal cell remains. Both benign and malignant tumors may undergo cystic degeneration. Hemorrhage into the pancreas and necrosis of the pancreas often result in a cyst. Cysts frequently have followed acute pancreatitis. The size of the cyst varies, and in the author's series, the largest one contained 2 gallons of fluid. The most frequent location was the head of the pancreas. The wall of the cyst was generally fibrous, but some contained an epithelial lining of the cylindrical type. As the cysts enlarged the epithelium usually disappeared. Diabetes did not follow in his series.

N. ENZER.

PARTIAL OBSTRUCTION OF THE RENAL ARTERY: DIMINISHED BLOOD FLOW: DIMINISHED INTRARENAL PRESSURE AND OLIGURIA. F. HINMAN and A. B. HEPLER, Arch. Surg. **11**:649, 1925.

Partial obstruction of the renal artery lowers the intrarenal blood pressure, and reduces the blood flow through the kidney. When this is combined with ureteral obstruction the degree of hydronephrosis is greater than that produced by simple obstruction of the ureter.

N. ENZER.

HIRSCHSPRUNG'S DISEASE, OR CONGENITAL MEGACOLON. O. HOFMANN and G. H. EWELL, Arch. Surg. **11**:674, 1925.

A case of enlargement of the colon in a boy 8 years of age was noted at operation. From the clinical history and appearance at operation the authors conclude that the case was one of congenital megacolon. Death occurred on the thirteenth day after operation, but necropsy was not obtained. They review the literature on the etiology, pathology and clinical treatment.

N. ENZER.

RENAL INJURIES BY AMINO ACIDS. L. H. NEWBURGH and P. L. MARSH, Arch. Int. Med. **36**:682, 1925.

Amino acids, arginine, aspartic acid, lysine, histidine, tyrosin, tryptophane and cystine are nephrotoxic.

AUTHORS' SUMMARY.

THE INFLUENCE OF HIGH PROTEIN DIET ON THE KIDNEYS. A. JAMES MILLER, J. Exper. Med. **42**:897, 1925.

Seven groups of rats were fed on diets containing protein varying in amount from 1.36 to 40.13 per cent derived mainly from grain, casein, meat, and milk with carbohydrate, fat and vitamins. From a number of animals one kidney was removed to double the load on the remaining one. The time of feeding was from nine weeks to six months. Blood uric acid, blood urea nitrogen determinations, and microscopic examinations of the kidneys revealed no evidence of kidney damage. There was evidence of kidney hypertrophy consisting of increased weight of the kidney, large diameters of the capillary tufts, convoluted tubules and kidneys in the animals receiving high protein diet. The nephrectomized animals that ate high protein had no kidney changes except hypertrophy, and this amounted to an increase in weight of an average of 0.54 Gm., or 85 per cent of the average weight of the right kidneys of the controls.

AUTHOR'S SUMMARY.

PERITONITIS OSSIFICANS. B. L. MEYERS, Surg., Gynec. & Obst. **41**:640 (Nov.) 1925.

A small mass of bony tissue was found at the tip of an atrophic appendix. It was surrounded by omentum and firmly fixed to the peritoneal coat of the appendix. Microscopically it showed atypical bone formation, and the appendix was subacutely inflamed with subacute peri-appendicitis. The author was unable to find a similar case reported in the literature.

N. ENZER.

FATTY TUMORS OF THE UTERUS. A. C. STARRY, Surg., Gynec. & Obst. **41**:642 (Nov.) 1925.

Seventeen cases of fatty tumors of the uterus were found in the literature, and the author adds an additional one. The tumor was intramural, and grossly and microscopically it exhibited large amounts of lobulated fat. He was unable to find fat droplets in definitely proved smooth muscle cells. The origin of the fat cells is either by metaplasia from connective tissue cells or from embryonic rests.

N. ENZER.

RUPTURE OF SEPTUM VENTRICULORUM. C. F. MARTIN and T. R. WAUGH, Ann. Clin. Med. **4**:183, 1925.

A case is described in a man, aged 52, previously in good health, the underlying condition being a gradual thrombosis in the left coronary artery on a probable syphilitic basis. The symptoms of septal rupture are discussed. The number of recorded cases is about twenty-five.

INCIDENCE OF BACTERIAL INFLAMMATORY PROCESS IN CARDIOVASCULAR DEFECTS: MALFORMED SEMILUNAR CUSPS. M. E. ABBOTT, Ann. Clin. Med. **4**:189, 1925.

The incidence of endocarditis in 555 cardiac anomalies from the literature is reviewed. The highest frequency is in malformed cusps and ventricular septal defects, then pulmonary stenosis and patent ductus. The conclusion is that endocarditis, mostly subacute, is extremely common in patients with cardiac defects who survive to maturity.

CALCIFICATION OF SUBCUTANEOUS TISSUE IN A CHILD (CALCINOSIS UNIVERSALIS). GUSTAV WILENS and JOSEPH DERBY, Am. J. Dis. Child. **31**:34, 1926.

A case of multiple calcifications of the subcutaneous connective tissue and fat, apparently unassociated with fat necrosis, is reported in a boy, 5 years old.

ON OSTEITIS DEFORMANS (PAGET'S DISEASE) AND ITS RELATION TO OSTEITIS FIBROSA AND OSTEOMALACIA. R. L. KNOGGS, Brit. J. Surg. **13**:206, 1925.

In a Hunterian lecture, Knoggs discusses the etiology, pathology and symptomatology of Paget's disease. Osteitis deformans, osteitis fibrosa, and osteomalacia are all considered to be produced by the action of the same group of toxins, probably metabolic or intestinal in origin. Osteitis deformans represents a strong reaction on the part of the osseous system to these toxins, and osteitis fibrosa a rather feeble reaction, while in the absence of the power to react, osteomalacia occurs.

LAWRENCE JACQUES.

A CONSIDERATION OF TWO CASES OF CYSTADENOMA OF THE PANCREAS, AND THEIR PROBABLE RELATIONSHIP TO POLYCYSTIC CONDITIONS FOUND IN OTHER VISCERA. E. R. CARLING and J. A. B. HICKS, Brit. J. Surg. **13**:238, 1925.

Two large cysts of the pancreas and one large solitary cyst of the stomach and pancreas are described. Microscopically they were strikingly similar. The authors point out further resemblances between these structures and the cysts of the liver, kidneys and spleen, and suggest a common origin from isolated portions of the wolffian body.

LAWRENCE JACQUES.

FAMILIAL XANTHOMA. J. LLAMBIAS and A. CELESIA, Rev. Soc. Arg. de biol. **1**:29, 1925.

A case of recurring xanthomas is reported in a young man (eye, elbows, knees, fingers and toes). The mother had flat xanthelasmas at the angle of both eyes, and the father presented a lipoma in the epigastrium. Five of the eight brothers of the patient also developed xanthomas at various points.

A GIANT APPENDIX CONTAINING A COLLECTION OF COLLOIDAL GRANULES (MYXOGLOBULOSE). EMILE C. MEGEVAND, Rev. méd. de la Suisse Rom. **45**:525, 1925.

The appendix described accords with others in the dilatation, the absence of recent inflammatory reaction, the complete obliteration of the opening to the cecum and the content of thick fluid with spherical colloidal granules. Such conditions are undoubtedly closely related to the pseudomyxomas with unformed colloidal masses. This peculiar formation into granules is explained

by Hansenmann as a result of the rubbing of the smooth wall without mucus over the mucus filament as it emerges from the lumen of the gland so that balls are formed much as starch granules are manufactured.

G. B. RHODES.

WHAT ARE THE RELATIONS BETWEEN EXUDATIVE AND PROLIFERATIVE TUBERCULOSIS? FERNAND CARDIS, Rev. méd. de la Suisse Rom. **45**:506, 1925.

There seems to be no essential difference between the exudative and proliferative types of tuberculosis which doubtless result from avirulent infection with weak resistance and from decreased virulence with increased resistance respectively. The peripheral zone because of its distance from the center of infection allows proliferation, and so mixed forms appear.

G. B. RHODES.

THE PATHOLOGIC-ANATOMIC DIFFERENCES BETWEEN PRIMARY TUBERCULOSIS OF THE TONSIL AND OF THE LUNG IN CHILDREN. C. RUF, Beitr. z. klin. Tuberk. **62**:286, 1925.

In a case of primary tuberculosis of the right tonsil in a 3½ months old child, the right cervical glands were found caseated, extending in a chain of decreasing size down to the angle between the anonymous and jugular vein. Here the gland had apparently ruptured into the blood stream, and a generalized miliary tuberculosis ensued. The other patient, a 2 year old child, had a primary focus in each upper lobe; the hilus glands were caseated; a chain of glands decreasing in size extended upward to the veinous angle; there were rupture and miliary tuberculosis as in the first case. The topography of the tuberculous glands made it possible to trace the infection back to the primary focus.

MAX PINNER.

PERITONEAL IMPLANTATION OF TISSUES. R. BENEKE, Beitr. z. path. Anat. u. z. allg. Pathol. **74**:2, 1925.

The work consisted of the immediate implantation of small bits of spleen, liver, suprarenal, heart and kidney of freshly killed normal rabbits into the peritoneal cavity of other rabbits. The purpose was to study the effects of aseptic autolysis, as influenced by the chemical changes in the different kinds of tissues, on the exudative and proliferative inflammatory reaction. The implanted tissues were removed at varying intervals of from two to five days and examined microscopically. Fibrin deposition was equal over the various tissues. Leukocytic infiltration was marked, and, although showing less difference in degree than expected, was greatest in and about the heart muscle. Karyolysis proceeded more slowly in the myocardial and suprarenal tissues than in the others. The proliferative reaction was equal over the different tissues, the newly formed tissue being derived chiefly from the host but also in part from surviving connective tissue cells of the implant. Applying his findings to aspetic infarction within the organs of the body, Beneke concludes that it is the function of the leukocytes to render harmless the irritative products resulting from autolysis, and that the separation or sequestration of the dead from the living tissue is brought about by the zone of organization.

O. T. SCHULTZ.

THE INTERSTITIAL CELLS OF THE TESTIS. F. BATTAGLIA, Virchows Arch. f. path. Anat. **257**:662, 1925.

Battaglia concludes that the increase in the testicular interstitial cells of Leydig, reported by Steinach and others as the result of ligation of the vas and of other conditions which cause a disappearance of the cellular elements of the spermatic tubules, is apparent and not real. An increase of lipoid containing cells occurs, but most of such cells are histiocytes which have secondarily phagocytized lipoid substances resulting from the destruction of seminal tubule cells. Such lipoid filled histiocytes have been termed lipoid interstitial cells by Ciaccio.

O. T. SCHULTZ.

Pathologic Chemistry

HYPERCHOLESTEROLEMIA. F. WILLIAM SUNDERMAN and FRED D. WEIDMAN, Arch. Dermat. & Syph. **12**:840, 1925.

Reports of chemically controlled hypercholesterolemias in the various experimental animals are surprisingly rare in the literature, giving scant basis for general conclusions. Of the common laboratory animals, the rabbit appears to be the most susceptible to experimental hypercholesterolemia and has been the most extensively used. As Luden intimates, this may be the expression of the herbivorous animal. If so, the rabbit should not be considered as the ideal experimental animal when comparing results with human disease, even though it be the animal of choice for inducing a hypercholesterolemia.

On oral feeding, a hypercholesterolemia may be induced in rabbits with almost any substance rich in cholesterol. Neutral fats do not suffice.

Subcutaneous injections have not had a fair trial as controlled by blood analyses.

The intravenous route may be employed, using either oil to emulsify the cholesterol or the emulsion of Dewey. The hypercholesterolemia thus induced is temporary (determined in rabbits only).

The intraperitoneal route provides a hypercholesterolemia of 25 per cent, lasting up to six weeks, provided coarse crystals are used.

AUTHORS' SUMMARY.

RESEARCHES ON INSULIN. I. IS INSULIN AN UNSTABLE SULPHUR COMPOUND? JOHN J. ABEL and E. M. K. GEILING, J. Pharm. & Exper. Therap. **25**:423, 1925.

By simple and noninjurious methods we have separated from Iletin (Lilly) (eight and twelve rabbit units per milligram) crystalline amino acids, protein-like fractions of varying sulphur content and low phosphorus content, and such as have a medium or relatively low sulphur content and a high phosphorus content. The active insulin can be completely removed from each of these fractions so that they no longer show a trace of the characteristic hormone. In the course of the purification the insulin rabbit unitage was raised from 8 and 12 to more than 40 in our Fractions IV.

Proof is furnished that when an "insulin" of high unitage is boiled for a short time with n/10Na_2CO_3 the resultant physiologic inactivation is always associated with an alteration in the linkage of a part, if not all, of the sulphur of the hormone. Ammonia is not liberated by this treatment. It has been

shown that our inert fractions contain very little of this labile sulphur, and in all fractions the content of labile sulphur, more especially what we have called the "sodium carbonate sulphur," appears to be directly proportional to the degree of hypoglycemic activity; that is to say, the higher the amount of "sodium carbonate sulphur" present in a given preparation, the higher is its potency.

Phosphorus is not a constituent of insulin.

The significance and implications of the observations relating to the labile sulphur are referred to in part in the paper.

It is hoped that our observations may serve as the basis for a chemical method for the assay of insulin.

AUTHORS' SUMMARY.

THE DIAGNOSTIC VALUE OF THE CEREBROSPINAL FLUID SUGAR CONTENT. W. P. STOWE, J. Lab. & Clin. Med. **11**:307, 1926.

While few compilations of figures seem available on normal fluids, the general trend of recent literature is to raise the figure ascribed to sugar content considerably above that given by the earlier French workers and by Foster, and place it in the neighborhood of 75 mg. per hundred cubic centimeters.

When series of cases of neurosyphilis, epidemic encephalitis and other neurologic and nonneurologic conditions, other than the meningitides, are examined, their deviation from the normal range and median point is found to be so slight as to be without diagnostic significance.

Tuberculous meningitis gives values so definitely above the purulent meningitis cases and so definitely below all other conditions that an almost certain diagnosis can be made quickly in this disease.

The occasional purulent fluids obtained after intraspinal therapy, in cases of brain tumor with necrosis or hemorrhage near the ventricles, in sympathetic aseptic meningitis, etc., can be rapidly delimited by their normal sugar content from infective meningitis in which the causative organism may not be promptly found. The presence of pus cells alone in the cerebrospinal fluid does not reduce its sugar content.

Two of the cases are interesting in that obstruction to the flow of cerebrospinal fluid at the base of the brain in the one and at the lower dorsal spinal level in the other did not produce any essential difference in the sugar content above and below the lesion. This would suggest that the diffusion of sugar into the cerebrospinal fluid occurs throughout the cerebrospinal axis rather uniformly and not through the choroid plexus alone.

AUTHOR'S SUMMARY.

THE FATTY ACIDS IN THE SUBCUTANEOUS FAT OF MAN. H. C. ECKSTEIN, J. Biol. Chem. **64**:797, 1925.

The ratio of liquid to solid fatty acids in the subcutaneous fat from the abdomen of man is similar to that reported by others for the fat of the blood and feces. The depot fat contains in excess of 0.5 per cent of linoleic acid, 0.33 per cent of an acid containing four double bonds and 0.03 per cent of an acid containing three. About 1 per cent of myristic acid and traces of tannic acid are probably present. The cholesterol content is 0.24 per cent.

ARTHUR LOCKE.

A Comparison of the Concentrations of Inorganic Substances in Serum and Spinal Fluid. B. Hamilton, J. Biol. Chem. **65**:101, 1925.

The concentrations of chloride, bicarbonate, inorganic phosphorus, total fixed base and calcium in serum and spinal fluid do not deviate from the normal in epilepsy. The ratios:

$$\frac{([Cl] + [HCO_3]) \text{ in fluid}}{([Cl] + [HCO_3]) \text{ in serum}} \text{ and } \frac{\text{Monovalent base in fluid}}{\text{Monovalent base in serum}}$$

are fairly constant and usually correspond. The ratio:

$$\frac{[HCO_3] \text{ in fluid}}{[HCO_3] \text{ in serum}} \text{ is variable.}$$

Arthur Locke.

Comparative Sugar Content of Blood and of Cerebrospinal Fluid in Various Conditions. A. Levinson, Am. J. Dis. Child. **30**:774, 1925.

In the nonmeningitic fluid the sugar varied between 50 and 76 mg. per hundred cubic centimeters of fluid; the amount of sugar varied from day to day and bore no relation to the blood sugar. In meningitis the sugar in the arachnoid fluid was low.

Importance of the Lipins and Their Relations to Cellular Equilibrium. M. Rubner, Klin. Wchnschr. **4**:1849, 1925.

A review.

Arthur Locke.

The Potassium Content of Blood and the Potassium to Calcium (K/Ca) Ratio in Essential Hypertony. E. Kylin and G. Myhrman, Klin. Wchnschr. **4**:1870, 1925.

The normal K/Ca quotient varies from 1.70 to 2.15. In instances of essential hypertony it varies from 2.08 to 2.97.

Arthur Locke.

The Influence of Renal Function on Cholesterol Metabolism. W. N. Nekludow, Ztschr f. ges. exper. Med. **47**:70, 1925.

Ligation of ureters or extirpation of the kidney results in a progressive increase of the cholesterol content of the blood up to the death of the animal. The increase is more marked after extirpation than after ligation.

S. A. Levinson.

Alterations of Blood Sugar with Altered Sugar Concentrations and in Pathologic Conditions of the Intestines. T. Ichihashi, Sc. Rep. Govt. Inst. Infect. Dis., Tokio **3**:181, 1924.

In a series of experiments on rabbits it was found that the rate of absorption of swallowed dextrose as measured by blood sugar content is diminished in diarrhea caused by sodium sulphate or croton oil, as well as in obstipation induced by the administration of astringents. In general, isotonic solutions were absorbed more rapidly than others.

H. E. Eggers.

Microbiology and Parasitology

EXPERIMENTAL STUDIES WITH A SPIRAL ORGANISM FOUND IN A WILD RAT AND IDENTICAL WITH THE ORGANISM CAUSING RAT-BITE FEVER. H. MOOSER, J. Exper. Med. **42**:539, 1925.

The spiral organism isolated from a wild rat has proved identical with that from a human case of rat-bite fever in Mexico City. Rabbits can easily be infected with these organisms. The subcutaneous inoculation of them is followed after from three to five days by a local edema, induration and inflammation: the primary lesion. About eight days after the appearance of the primary lesion, edematous swellings and inflammation appear on the head and genitals: the secondary lesions.

The organism can be transmitted from rabbit to rabbit by coitus.

Protective antibodies are to be found in the blood of infected rabbits at a time when the local lesions are still active. The peculiar character of certain lesions probably is due to the escape of the antibodies from the blood stream.

The organism belongs to the genus *Spirochaeta*.

AUTHOR'S SUMMARY.

BACTERIOPHAGE TESTS ON THE MECONIUM OF ABORTED FETUSES. EVERETT S. SANDERSON, J. Exper. Med. **42**:561, 1925.

The theory that tissue cells are the source of bacteriophage was objected to by d'Herelle on the grounds that bacteriophage in the intestinal contents could penetrate the intestinal mucosa and migrate throughout the body and that any demonstration of its presence within the body fluids was in accordance with this phenomenon. The present work sought to overcome this objection by using tissues which had been exposed to but a single organism *Bacillus abortus*. Filtrates of meconium from six aborted bovine fetuses were tested against several strains of *Bacillus abortus*, but no evidence of a lytic principle could be demonstrated. Neither could it be shown that they contained a substance which would initiate lysis when tested against numerous strains of bovine colon bacilli.

AUTHOR'S SUMMARY.

STUDIES ON BRUCELLA (ALKALIGENES) MELITENSIS. I. THE SEROLOGIC CLASSIFICATION OF STRAINS FROM HUMAN, BOVINE, CAPRINE, PORCINE, AND EQUINE SOURCES. ALICE C. EVANS, Hyg. Lab. Bull. **143**:1, 1925.

The agglutinin absorption tests with sixty-eight strains of *Brucella melitensis* showed that the species may be differentiated into at least eight serologic groups. Three of these groups included only one strain each. The majority of bovine and porcine strains fell into one large group (thirty-three strains), which is designated variety abortus. Five strains of human origin were of this variety. Another group important in this country includes strains of human, bovine, caprine, and equine origins (twelve strains). It is designated variety melitensis A. Three groups which were found to be prevalent in Mediterranean countries did not occur among the strains received from countries outside of those regions. One of these groups is designated variety *Br. melitensis* B; another, which corresponds with the descriptions of the so-called paramelitensis is designated variety paramelitensis; another serologic group is designated para-abortus, because it is serologically closely related to the abortus variety, and exhibits agglutination peculiarities like those of the variety paramelitensis.

Simple agglutination tests cannot distinguish the varieties of *Br. melitensis*.

AUTHOR'S SUMMARY.

STUDIES ON BRUCELLA MELITENSIS. IV. CATTLE AS A SOURCE OF HUMAN INFECTION. ALICE C. EVANS, Hyg. Lab. Bull. **143**:36, 1925.

A review is given of the literature on (*a*) cases of Malta fever which could not be traced to infection from goats; (*b*) the prevalence of *Br. melitensis* in cow's milk; (*c*) infectiousness of bovine strains of *Br. melitensis* for man; (*d*) titers considered indicative of *Br. melitensis* infections in man; (*e*) specificity of the serum reaction with *Br. melitensis*.

Five hundred human serums from patients suffering with a variety of diseases were tested for agglutinins specific to *Br. melitensis*. Fifty-nine, or 11.8 per cent, gave a definitely positive reaction in dilutions of 1:5 or higher.

One serum had a titer of 1:320, which would lead to an unquestioned diagnosis of Malta fever in regions in which the disease is endemic. The patient was unaware of any possibility of having contracted an infection from goats. He was in the habit of drinking raw cow's milk. Absorption tests with the serum indicated that this patient was infected with the abortus (bovine) variety of *Br. melitensis*.

The titers of the remaining fifty-eight serums which gave positive reactions varied from 1:15 to 1:40. The suggested explanation for these positive reactions is that the agglutinins were produced as a specific response to *Br. melitensis* ingested in cow's milk, although such an infection may not necessarily have caused a notable illness.

A description is given of the methods used for the identification of the variety of infecting organism.

AUTHOR'S SUMMARY.

ENLARGEMENT OF THE SPLEEN IN MEASLES. ADRIEN BLEYER, Am. J. Dis. Child. **31**:26, 1926.

Enlargement of the spleen was found to occur in a majority of two independent groups of cases of measles seen during three succeeding winters in St. Louis, and numbering altogether almost 400 persons. This enlargement of the spleen was coincidental with the eruptive stage of this disease, both as to appearance and disappearance, the greatest enlargement both as to frequency and size being noted on the third and fourth days of the rash. Contrary to what might be expected, the severity of an attack in these patients did not seem to make the occurrence of enlargement of the spleen higher than in those that ran a milder course.

These three conclusions run together, and indicate that enlargement of the spleen in measles is directly related to the virus of this disease. It would, therefore, seem fit to include enlargement of the spleen in the symptomatology of measles.

AUTHOR'S SUMMARY.

STUDIES ON RESPIRATORY DISEASES. XXV. THE INFLUENCE OF CERTAIN ELECTROLYTES AND NONELECTROLYTES ON THE BILE SOLUBILITY OF PNEUMOCOCCI. I. S. FALK and S. Y. YANG, J. Infect. Dis. **38**:1, 1926.

Washed suspensions of pneumococci in distilled water are usually bile soluble. An occasional preparation is refractory to the solvent action of the bile.

Chlorides with monovalent cations (Na, K, NH_4, Li) in relatively low concentrations inhibits solution of washed pneumococci by bile. In higher concentrations these chlorides do not inhibit and may accelerate the dissolution of the bacteria.

Chlorides with divalent cations (Ca, Ba) behave differently. They are found to inhibit bile solution of pneumococci more effectively in high than in low concentrations. Of the amion series tested, NaOH and Na_3PO_4 are cytolytic to pneumococci; Na_2HPO_4, NaH_2PO_4, Na_2SO_4 and $NaNO_3$ are not cytolytic. Cytolysis by NaOH and Na_3PO_4 appears to be a function of hydroxyl ion concentration. Peptone, gelatin and ovalbumin appear to inhibit cytolysis by bile in the same manner as $CaCl_2$ and $BaCl_2$. The inhibitory action increases with concentration.

The differences in the behavior of chlorides of monovalent and of divalent cations recorded here appear to be in harmony with the usual findings in general physiology, whether effects on animals and animal tissues, on chlorophyll-bearing plants, bacteria or on nonliving substances are studied. These general relations have been discussed at length by Falk. Their bearing on the mechanism of bacteriolysis will be treated in a later publication from this laboratory.

AUTHORS' SUMMARY.

STUDIES ON RESPIRATORY DISEASES. XXVI. THE LYSIS OF PNEUMOCOCCI BY SODIUM OLEATE. I. S. FALK and S. Y. YANG, J. Infect. Dis. **38**:8, 1926.

In concentrations of 1.25 per cent and higher, pure solutions of sodium oleate in water are bacteriolytic to washed suspensions of pneumococci of types 1, 2 and 3. Saponin in concentrations of 0.5 to 10 per cent in 0.85 per cent sodium chloride does not dissolve pneumococci.

In the concentrations in which it is active, sodium oleate dissolves only pneumococci of those strains which are also dissolved by bile. Sodium oleate, in effective concentrations in water, dissolves washed pneumococci resuspended in distilled water. It does not dissolve washed pneumococci which have been resuspended in 0.85 per cent sodium chloride solution or in the supernatent of the culture fluid from which they had been separated by centrifugalization.

In the concentrations used in the experiments reported, the bacteriolysis of washed pneumococci by sodium oleate, sodium hydroxide and sodium phosphate (tribasic) is as specific as bile solubility. Suspensions of bile insoluble strains of pneumococci of strains of hemolytic streptococcus, *Str. viridans, Str. lacticus, Neisseria catarrhalis, Sarcina lutea, Staphylococcus albus* and of *Staph. aureus* are not dissolved by these reagents.

It appears that the dissolution of pneumococci by bile, sodium oleate, sodium hydroxide and sodium phosphate is determined as definitely by the specific characteristics of these bacteria as by the properties of the solvent agent.

Because of the chemically pure state in which it can be prepared and its certain composition, sodium oleate may serve useful purposes in bacteriolytic experiments with pneumococci in which bile of uncertain and variable composition is now generally used.

The bacteriolytic action of soaps — as typified by sodium oleate — is specific to pneumococci among the bacteria studied. Hence, we are of the opinion that the functional rôle of these substances is not of general significance in bacteriolytic phenomena of pathology.

AUTHORS' SUMMARY.

THE MECHANISM OF THE RUSSELL DOUBLE SUGAR TUBE. MILTON W. HALL and GEORGE R. LACY, J. Infect. Dis. **38**:14, 1926.

While the acids produced in the fermentation of dextrose in the Russell double sugar medium are mainly, if not entirely, volatile, their diffusion out of the medium is not the cause of the alkaline reaction shown on the slant

when typhoid and related organisms are grown. This reaction is due to excess of alkaline substance produced from nitrogenous elements in the presence of oxygen.

In the absence of oxygen a "mother substance" is formed, which rapidly becomes alkaline when exposed to oxygen. The ultimate alkaline reversion in the butts of Russell tubes is the result of the diffusion into the butts of oxygen rather than of the alkali formed in the slant portion of the tube.

The paratyphoid and colon groups appear capable of producing an alkaline reacting substance under anaerobic conditions, thus evidencing a definite difference in metabolism which may prove worthy of further study.

No suggestion is made as to the chemical nature of the substance which is so easily oxidized into an alkaline substance.

AUTHORS' SUMMARY.

OBSERVATIONS ON 6,500 CASES OF LOBAR PNEUMONIA AT THE COOK COUNTY HOSPITAL, CHICAGO. FRANK B. KELLY, J. Infect. Dis. **38**:24, 1926.

In the seven and one-half years from Jan. 1, 1917, to July 1, 1924, there were 6,531 cases of lobar pneumonia at the Cook County Hospital, Chicago, with a case fatality of 36 per cent.

The case fatality in the individual years varied between 34 and 41.4 per cent with the exception of 1921 when only 26.6 per cent died. The decrease in 1921 occurred in both sexes, in negroes and in white persons, and in all age groups. The death rate from this infection was markedly lower in the entire country in that year. There was no significant difference in the case fatality for the entire period in the two sexes. The case fatality among the negroes was from 5 to 13 per cent below that of the whites in the different years. This was due to a lower case fatality in the negroes in the "40 years and over" group. The case incidence among the negroes in Chicago during this period was apparently twice that of the whites.

The age incidence in the 6,531 cases showed a large number in the "under 5 years" group, the fewest in the second decennium, with a steady increase through the "40 to 49 year" group, followed by a decline so rapid that the number in the "60 year and over" group was very small. The case fatality was lowest in the "5-9 year" group, and from that point increased proportionately with the age.

The greatest number of persons with lobar pneumonia entering the hospital during the year was during the months of January through April. The lowest number was in August. The greatest case fatality was in October, the lowest in June, the variation throughout the composite year being from 32.4 to 41.8 per cent.

There was only 5 per cent difference in the total number of case fatalities of the separate wards for the entire period. Differences in individual years were not accounted for on a basis of age.

AUTHOR'S SUMMARY.

A METHOD FOR TRANSFERRING TUBERCLE BACILLI FROM SOLID TO LIQUID CULTURE MEDIA. A. LUTZ, Am. Rev. Tuberc. **10**:270, 1925.

To overcome the technical difficulty of transferring tubercle bacilli from solid to liquid mediums, the following technic is recommended: "Solid medium slants are made in 100 cc. Erlenmeyer flasks by pouring in 50 cc. of glycerine agar while in a liquid state. This is properly sterilized, and the flask is placed in such a position as to allow the medium to harden into a slant that runs

from just below the mouth to the bottom of the flask. When hardening has taken place, 15 cc. of sterilized glycerine broth are added." The agar slant is heavily seeded with bacilli down to the fluid level and incubated. At the end of three weeks usually the surface of the liquid is covered by bacilli.

MAX PINNER.

SCREW WORMS FROM SOFT PALATE. L. S. GAUDET, South. M. J. **18**:824, 1925.

A perforation through the central part of a swelling in the soft palate was filled with screw worms (larvae of the fly *Compsomyia maellaria*) burrowing in all directions. Sixty-two worms were removed.

TYPHOID INFECTIONS OF KIDNEY. F. S. PATCH, J. Urol. **14**:199, 1925.

Two cases of pyonephrosus due to *B. typhosus* are reported by Patch, and eight cases from the literature are reviewed. In both of Patch's cases, the disease was unilateral. There was nothing to indicate the exact time of onset in either case. Masses of calculi were found scattered in the calices in one of the cases. Patch believes that typhoid infections of the kidney are more common than has generally been believed. They must be regarded as of hematogenous origin.

AN EXPERIMENTAL INVESTIGATION OF THE SUPPOSED RELATION BETWEEN GOOD PHYSICAL CONDITION AND NATURAL RESISTANCE TO INFECTION. REYNOLD A. SPAETH, Am. J. Hyg. **5**:839, 1925.

White female rats in a good physical state as a result of spontaneous exercise, survived infections with pneumococci less well than unexercised control rats. Young starved guinea-pigs and exhausted guinea-pigs resisted pneumococcus infections better than normal pigs. It is suggested that natural resistance is in part at least a function of the anabolic rate.

THE MICROORGANISM OF CONTAGIOUS AGALACTIA. J. BRIDRE and A. DONATIEN, Ann. de l'Inst. Pasteur **39**:925, 1925.

Contagious agalactia of sheep and goats is caused by an organism culturally and biologically similar to the organism of peripneumonia in cattle described by Bordet. It is a visible but filtrable organism, pleomorphic, aerobic or anaerobic, growing in mediums containing serum or in milk. It remains viable and virulent for many months in anaerobic conditions, and is virulent only for sheep and goats. Vaccination is not successful in all conditions, but a protective serum has been prepared.

G. B. RHODES.

ON COCCIDIA AND COCCIDIOSIS OF THE RABBIT. III. STUDY OF ENDOGENOUS MULTIPLICATION. C. PERARD, Ann. de l'Inst. Pasteur **39**:952, 1925.

There are described three species of coccidia belonging to the genus *Eimeria*. One is found only in the biliary ducts and the other two are found in the small intestine.

G. B. RHODES.

FOUR YEARS OF VACCINATION AGAINST CHICKEN CHOLERA. A. STAUB, Ann. de l'Inst. Pasteur **39**:962, 1925.

A suitable method of vaccinating fowls against chicken cholera consists in a primary injection of living cultures of a rabbit pasteurella followed by

vaccination with a partially attenuated strain of chicken cholera. The latter if used alone often manifests a marked virulence, but it confers a more lasting immunity than the rabbit pasteurella, which, however, has a decided prophylactic value and confers an immediate immunity.

G. B. RHODES.

BACTERIOPHAGE IN THE NEW-BORN. R. PIERRET and V. BILONET, Compt. rend. Soc. de biol. **93**:635, 1925.

No bacteriophage for Shiga, colon or typhoid bacilli could be detected even in meconium rich in micro-organisms of eight new-born infants up to 4 days old. The bacteriophage content was excessive in the stool of an infant 12 days old.

HISTOPATHOLOGY OF EXPERIMENTAL ACUTE POLIOMYELITIS (HEINE-MEDIN) OF MONKEYS AND GUINEA-PIGS. HANS GERHARD CREUTZFELDT, Ztschr. f. Hyg. u. Infectionskh. **105**:402, 1925.

Creutzfeldt gives a description accompanied by photomicrographs of the lesions in the spinal cords of the animals used by Picard in his experiments. He emphasizes the importance of edema in the development of the changes. He also comes to the conclusion that in monkeys the neuronophagia is not performed by leukocytes but by glia cells (Hortega cell).

W. OPHÜLS.

MECHANISM OF IMMUNITY TO STREPTOCOCCI. FRANZ BASS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **43**:269, 1925.

Injections of streptococci into the bone marrow and pleural cavities indicate that the chief mechanism of immunity to streptococci is in the phagocytosis and destruction of them by the reticulo-endothelial cells. Immune serum acts on these cells in the same way as it does on leukocytes.

JEAN OLIVER.

ANTHRAX. E. SINGER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **43**:285, 1925.

Anthrax bacilli are taken up and destroyed by the reticulo-endothelial cells. In immunized animals this destruction is complete. In normal animals the bacilli proliferate in the cells, escape from them and secondarily invade the blood stream.

JEAN OLIVER.

THE THEORY OF MEASLES AS A REACTION SICKNESS. W. KELLER and E. MORO, Klin. Wchnschr. **4**:1719, 1925.

Illnesses which owe their origin to the action of the body's specific reaction products on the pathogenic substance are defined as "specific reaction sicknesses," and are especially typified by measles in contrast to diseases such as scarlet fever, diphtheria, etc., which have no normal incubation period and are due primarily to the action of toxins. An antitoxic substance exists in reconvalescence serum in addition to the bacteriolysins. The course of measles is first building up of bacteriolysins, and finally, building up of antibodies for the endotoxins released in the ensuing bacteriolysis.

ARTHUR LOCKE.

Immunology

FURTHER STUDIES ON A DIPLOCOCCUS IN MEASLES. A MEASLES SKIN REACTION. RUTH TUNNICLIFF, J. Infect. Dis. **37**:193, 1925.

Anaerobic dextrose broth cultures of the green-producing diplococcus found in measles killed by 0.5 per cent phenol appear to produce a skin reaction in persons who have not had measles, but not in measles patients after the appearance of the eruption, or in 96 per cent. of persons who give a history of measles. The measles antigen is neutralized in persons who have not had measles by convalescent human measles serum, but not by the serum of a person with a negative history of measles. Reaction occurs also in normal rabbits, while rabbits immunized against measles fail to react. The measles antigens are neutralized in rabbits by convalescent human measles serum and by the serum of goats recovering from the reaction produced by measles diplococci, but not by normal goat serum. Green-producing cocci from other sources generally give no reactions in rabbits, but the strains that do produce similar reactions in both immune and nonimmune rabbits are not neutralized by convalescent human measles serum. Normal rabbit serum neutralizes measles antigen partly; immune rabbit serum completely neutralizes it.

These results indicate that the gram-positive green-producing diplococcus found in measles is of etiologic significance.

AUTHOR'S SUMMARY.

THE PROTECTIVE SUBSTANCE IN ANTIPNEUMOCOCCIC SERUM. LLOYD D. FELTON, J. Infect. Dis. **37**:199, 1925.

The protective antibody in type 1 antipneumococcic serum, so far studied, is in large part associated with a water-insoluble globulin, which is precipitated by dilution 1:10 in water or with water acidulated by varying amounts of hydrochloric, o-phthalic, phosphoric, tartaric, citric acids in a range of hydrogen ion concentrations between p_H 5.5 and p_H 7.8. The optimum hydrogen ion concentration for precipitation when the serum is diluted 1:10 has not been definitely determined.

The amount of protective substance obtained in diluting serum 1:10 is apparently increased by the use, in concentration of two hundredth molar to four hundredth molar, of phosphate buffers. The single sample of serum precipitation of type 1 antibody by 50 per cent. saturation with ammonia sulphate failed to give a yield as high as simple dilution with water 1:10. Chloroform denatures globulin and destroys the protective action of antibody to a degree corresponding to the extent of the removal of protein from the solution. Extraction with ether in acid or sodium chloride solution destroys a considerable part of the protective value of this globulin, while in alkaline solution five hour extraction has little or no effect.

An apparent exception to the association of the protective body with the water-insoluble fraction of serum is given in the case of a sample of horse serum possessing protective value, but yielding little protective precipitate. In relatively abundant precipitates, there seems to be a direct relation between the protective value of the precipitate and the yield. The precipitate obtained by dilution of serum from horses immunized but a short time has less protective value per milligram of nitrogen than the precipitate from horses immunized over a longer period. Heat alters the type 1 antipneumococcus serum so that no precipitate results from dilution with 10 volumes of distilled water. On the addition of acid, a precipitate is formed which has less protective power than the unheated control.

QUANTITATIVE CHANGES IN BLOOD SUGAR AND BLOOD LACTIC ACID IN CANINE ANAPHYLAXIS. MARGERY MCCULLOUGH and FRANCIS I. O'NEILL, J. Infect. Dis. **37**:225, 1925.

Horse serum injected intravenously into normal dogs causes a gradual increase in the sugar content of the blood, the blood sugar rising to about twice the normal percentage by the end of two hours. This increase indicates a toxic action of the horse serum on normal dogs, not shown by changes in arterial blood pressure, the currently used index in canine anaphylaxis. Horse serum injected intravenously into "negatively sensitized" dogs causes no changes in blood sugar during the first two hours. These dogs, therefore, are resistant to the normal toxicity of horse serum, and should be regarded as immune.

During typical canine anaphylactic shock, the blood sugar increases rapidly, reaching nearly twice the normal concentration by the end of twenty minutes. The blood sugar then gradually decreases, being but slightly above normal by the end of two hours. After the first fifteen minutes, the curve thus obtained is identical with the blood sugar curve obtained by intravenous injection of an amount of glucose equivalent to the total estimated glycogen content of the liver. During typical canine anaphylactic shock the blood lactic acid increases to twice the normal concentration within the first thirty minutes, gradually falling to about 40 per cent above normal by the end of two hours.

NONSPECIFIC STIMULATION OF A NATURAL ANTIBODY. T. J. MACKIE, J. Hyg. **24**:176, 1925.

The natural hemolytic antibody of the rabbit for sheep blood is constant in amount in normal, healthy rabbits, and may remain unaltered after extensive bleedings. There is a marked increase in the concentration of the antibody after successive large bleedings. Small bleedings have no such effect. The antibody is increased in amount following the injection of certain nonspecific substances: metallic salts ($MnCl_2$, $BeCl_2$), colloidal manganese, arsphenamine, sodium nucleinate, and normal ox serum. The effect is inconstant and variable in degree. The increase produced is less than that obtained by immunization with the homologous or even with heterophile antigen.

ARTHUR LOCKE.

COMPLEMENT FIXATION IN TUBERCULOSIS. III. STUDIES ON THE NATURE OF THE ANTIGEN. M. PINNER, Am. Rev. Tuberc. **12**:154, 1925.

Comparative titration of more than seventy preparations derived from tubercle bacilli proved that the main complement-fixing substances are closely associated with that fraction of the bacilli which is practically insoluble in acetone, ether and chloroform and soluble in alcohol.

It is felt that no proof has been given that the alcohol-soluble substances contain the only antigenic principle, but no tubercle bacillus extract from which these substances have been removed retained a sufficient amount of antigenic power to make it fit as an antigen in complement fixation.

Evidence has been introduced that the degree of dispersion plays an important rôle in the antigenic value of lipoidal tuberculous antigens.

The protein substances exert an inhibiting influence on the lipoids in complement fixation.

No evidence has been found for the assumption that certain serums from tuberculous patients react only with protein and others only with lipoidal antigens.

S. A. LEVINSON.

EFFECT OF ROENTGEN RAYS ON ANTIGENIC SPECIFICITY OF CERTAIN PROTEINS EXPOSED IN VITRO. C. H. LING, J. Cancer Res. **9**:305, 1925.

The proteins, represented by *B. typhosus*, by horse serum and by sheep erythrocytes when exposed in vitro to large doses of unfiltered roentgen rays, Ling found, do not lose their antigenic specificity as tested by the production of immune serums in rabbits. Agglutinins, precipitins and hemolysins produced by irradiated antigens appear identical with those produced by the nonirradiated antigens in each instance.

ANAPHYLAXIS WITH BACTERIAL EXOTOXIN. BRUNO POLETTINO, Boll. d. Inst. sieroterapico Milanese **4**:197, 1925.

Intravenous injection of diphtheria toxin into rabbits completely immunized with broth and killed and washed diphtheria organisms produces anaphylaxis. The conclusion is thereore that diphtheria exotoxin is a truly anaphylactic substance.

E. B. PERRY.

VACCINATION AGAINST DYSENTERY BACILLI SHIGA-KRUSE TYPE. FERDINANDO COLOMBO, Boll. d. Inst. sieroterapico Milanese **4**:233, 1925.

Specific precipitins and definite immunity were produced in both men and animals by the injections of young cultures of the Shiga-Kruse dysentery bacillus. These cultures, suspended in physiologic sodium chloride, slightly acidified, killed by heat at not over 50 C. for about one hour, and then neutralized before injections, were well tolerated.

E. B. PERRY.

EXISTENCE OF HETEROGENETIC ANTIGEN IN RED CELLS FREED FROM PLASMA. X. FRIDE and F. GRUENBAUM, Arb. a. d. Microbiol. Inst. d. Volksunterrichtskomissariats **1**:100, 1924.

Sheep erythrocytes, along with homologous and specific antigens for that species, or antigens of related animals or of the fowl and turtle, contain as well receptors for the cat — heterogenic antigens for the cat. Red cells of the cat together with specific antigens for that species contain heterogenic antigen for the sheep. Rabbits immunized with the sheep erythrocytes, together with the homologous agglutinins, produce heterogeneous agglutinins for cat erythrocytes.

During immunization of rabbits with cat erythrocytes there is a great production of the homologous agglutinin and very little of hemolysin. Heterogeneous agglutinins for sheep erythocytes are not produced by the process.

Heterogeneous immunity is connected not only with nucleoproteins but also with red cells freed from plasma. The law of Doerr and Pick is not applicable to the inverse relationships which exist between erythrocytes and organs of an animal in respect to their content of heterogenic antigen, with all animals. There are numerous animals which have heterogenic antigen both in organs and in red cells.

Animal cells contain a great number of biochemical complexes which are common to unrelated groups.

H. E. EGGERS.

HETEROGENEOUS PASSIVE ANAPHYLAXIS. L. KRITSCHEWSKI, Arb. a. d. Microbiol. Inst. d. Volksunterrichtskomissariats **1**:105, 1924.

Serum of rabbits immunized with fowl erythrocytes evokes with sheep erythrocytes the phenomenon of heterogeneous passive anaphylaxis when injected into normal rabbits.

H. E. EGGERS.

PRESENCE OF HETEROGENETIC ANTIBODIES IN NUCLEUS-FREE ERYTHOCYTES. K. A. FRIEDE and F. T. GRÜNBAUM, Klin. Wchnschr. **4**:1778, 1925.

Immunization with cat erythrocytes produces lysins for sheep erythrocytes and vice versa.

ARTHUR LOCKE.

ACTIVE IMMUNIZATION AGAINST DIPHTHERIA. R. KOCHMANN, Klin. Wchnschr. **4**:1914, 1925.

There is a negative phase, immediately after the injection of neutral toxin-antitoxin mixtures, when the susceptibility of the individual to the diphtheria bacillus is increased.

ARTHUR LOCKE.

CONCERNING THE EXISTENCE OF CELLULAR ANAPHYLAXIS. II. PASSIVE CELLULAR ANAPHYLAXIS IN DOGS. I. L. KRITSCHEWSKY and K. A. FRIEDE, Centralbl. f. Bakteriol., Parasitenk. u. Infektionsk. I., O. **96**:68, 1925.

Passive cellular anaphylaxis can be demonstrated in dogs under the same conditions as serum anaphylaxis in guinea-pigs and the heretofore doubtful cellular anaphylaxis in rabbits. The dogs received injections with immune serum, and at the same time or later, with the corresponding erythrocytes. The resulting anaphylactic shock was quite distinct. From this it can be concluded that cellular anaphylaxis is as real a fact as serum anaphylaxis.

B. R. LOVETT.

Tumors

NEOPLASM OF THE BLOOD—LYMPHVASCULAR SYSTEM WITH SPECIAL REFERENCE TO ENDOTHELIOMAS. D. S. PULFORD, Ann. Surg. **82**:710, 1925.

In a series of 200 tumors arising from the blood-lymph-vascular system 183 were angiomas, 9 angioendotheliomas and 8 endotheliomas. That angiomas are potentially malignant is illustrated by a case which developed from the benign angioma through the stage of angio-endothelioma and finally into endothelioma. The morphologic differences between these three types are chiefly increased cell growth and diminished vascular spaces in those which are developing toward endotheliomas. The literature on the subject, the various theories of the embryogenesis of endothelium and the influence of the "reserve" cells of McCarty on the development of endothelial tumors are reviewed.

N. ENZER.

THE EFFECT ON PARAMECIA OF BLOOD SERUM, ESPECIALLY FROM PATIENTS WITH CARCINOMA. G. A. DALAND, Arch. Int. Med. **36**:762, 1925.

Paramecia mixed with human blood serum form vesicles, the rate of formation being an index of the lethality of the serum.

No specific substance was found in the blood serum of patients with carcinoma which affected the rate of vesicle formation in paramecia in any way different from normal serum.

Serums from diseased persons may resemble those from normal subjects in their effects on paramecia, or their toxicity may be greater or less. Serum obtained at the time of menstruation is slightly more toxic than at other times.

Serums differing in their effects on paramecia may be made to act similarly by altering their concentration.

Diluted serums, serums containing hemoglobin or that have been heated, serums irradiated with ultraviolet light and serums of patients who have just received roentgen-ray therapy are all less toxic for paramecia than the control serums.

S. A. LEVINSON.

RELATIONSHIP OF ECTOPIC ADENOMYOMA TO OVARIAN FUNCTION. W. P. GRAVES, Am. J. Obst. & Gynec. **10**:665, 1925.

If one grants the endometrial and menstruating character of adenomyomas, it is logical to suppose that there must exist between the glandular structure and ovarian function the same endocrinal relationship that exists between the ovaries and the normal endometrium. Thus one should expect to find continued activity on the part of ectopic endometrium in the presence of functioning ovarian tissue and likewise atrophic regression of the same endometrium if the ovaries are completely ablated. Four cases are reported which support this theorem. In each the ectopic adenomyomatous tissue underwent regression following oophorectomy. Graves is convinced that in the majority of cases the endometriomas may be counted on to atrophy in the absence of ovarian function and that this is a valuable guide to treatment in cases in which operation is difficult.

E. S. GAIS.

ADENOMYOSIS UTERI. OSKAR FRANKL, Am. J. Obst. & Gynec. **10**:680, 1925.

The term adenomyosis uteri is applied by Frankl to the condition described by him in which there is penetration of the uterine mucosa, both glands and stroma, into the myometrium. No signs of an inflammatory origin were ever discovered, hence the objection to the terms adenometritis, adenomyositis, adenomyometritis. The condition should be differentiated from the rare true adenomyoma in which the glands originate independently within the myoma as an autochtonous growth. He emphasizes the occurrence of the condition in the preclimacteric and climacteric age and attributes its origin to a deficient resistance of the myometrium toward the penetrating endometrium, probably secondarily acquired. He cannot determine whether a lack of ovarian hormonic activity is a causative factor. The condition is rarely found in nullipara. The symptomatology is discussed and operative therapy advised.

E. S. GAIS.

MALIGNANT OVARIAN NEOPLASMS. WITH REPORT OF THE END-RESULTS IN A SERIES OF 56 CASES. CHARLES C. NORRIS and M. E. VOGT, Am. J. Obst. & Gynec. **10**:684, 1925.

Of 13,259 patients admitted, 1,028 were found to be suffering from ovarian tumors. In this series ovarian neoplasms constituted 7.7 per cent of all gynecologic lesions and 14 per cent of all gynecologic new growths. Of the ovarian tumors, 11.18 per cent were malignant, the most frequent of these being

glandular adenocarcinoma and papillary adenocarcinoma. Twenty-three per cent of the glandular adenocarcinomas survived three years after operation, as against 70 per cent of the papillary adenocarcinomas. The transtubal route of dissemination from a fundus carcinoma to the ovary and vice versa is possible. In these associated lesions the ovarian tumor is generally the larger regardless of which is primary. Primary malignant tumors are usually bilateral, and malignant degeneration of benign tumors tends to involve both ovaries. Seven per cent of pseudomucinous cysts and a smaller percentage of the dermoids showed carcinomatous change.

E. S. Gais.

Ultraviolet Absorption Spectra of Blood Serums in Relation to Infectious Diseases and Cancer. W. Stenstrom and M. Reinhard, J. Cancer Res. **9**:394, 1925.

Stenstrom and Reinhard assert that blood serum of animals and human beings shows absorption bands in the ultraviolet part of the spectrum. Blood serums from cancer patients were examined and showed a slight variation among themselves. However, no definite difference was discovered between normal persons and cancer patients. There was not a marked difference in the absorption spectra between serums taken before and immediately after roentgen-ray irradiation or between the absorption spectra taken before and after the serums had been irradiated in a test tube with a moderate dose of roentgen rays.

Autoplastic Implantation of Tar Tumors as Compared to Their Histologic Picture. L. Kreyberg, J. Cancer Res. **9**:381, 1925.

Ten autoplastic inoculations made by Kreyberg of tumors of histologically innocent appearance were all negative. Two autoplastic inoculations of tumors of histologically dubious appearance were negative. Ten out of thirteen autoplastic inoculations of tumors histologically malignant were positive. In these experiments a complete parallelism was found between the growth of the autoplasts and the histologic structure. It has not been possible to find any difference between the biologic and the histologic qualities of tumors tested.

A Consideration of the Hypophysial Adenomata. N. M. Dott and P. Bailey, Brit. J. Surg. **13**:314, 1925.

This paper is based on a clinical and pathologic study of 162 cases of hypophysial adenomas in the Brigham Hospital series to May, 1924. Although grossly the various types of tumor were indistinguishable, histologically they were divisible into chromophobe, chromophil, mixed, and malignant varieties. Chromophobe adenomas were the most common, comprising 107 cases of the series, and were associated clinically with the hypopituitary syndrome. Depression of sexual function was the earliest symptom to develop, atrophic changes of the skin and hair were constantly present, and a large proportion of the patients were obese; the basal metabolism averaged about 20 per cent below normal. Infantilism with this type of lesion was never observed, although it may frequently be the accompaniment of a craniopharyngeal pouch cyst. In contradiction to the increased sugar tolerance demonstrated by the alimentary test, the elevation of the blood sugar curve after the intravenous injection of glucose was found to be of longer duration than normal. The thirty-nine examples of eosinophilic adenomas in the group were constantly associated with the syndrome of overgrowth—gigantism or acromegaly. Skin, hair, and osseous

changes were the outstanding clinical features, while sexual depression, though frequently a symptom, was sometimes absent. The basal metabolism tended to be elevated, becoming as high as plus 30, but normal or subnormal rates were not uncommon. In 20 per cent of the cases a glycosuria was present, which was apparently due to the inadequate utilization of glucose. The thirteen tumors of a mixed type were associated with syndromes in which clinical evidences of both hypopituitarism and hyperpituitarism were present. No basophilic adenomas were encountered. There were three adenocarcinomas in the series, the constitutent cells of which contained no granules. In the one case which came to necropsy, metastases were found in the hepatic lymph nodes and liver. From a consideration of the pathologic and physiologic evidence at hand, the authors conclude that the pars distalis of the hypophysis exerts an influence on growth, and that the eosinophilic cells are the ones chiefly concerned. A brief introduction by Cushing precedes the article.

LAWRENCE JACQUES.

CONCERNING TAR TUMORS IN RABBITS. STANISLAW CIECHANOWSKI and J. MOROZOWA, Trav. d'Inst. d'anat. path. d. Univ. de Pologne **1**:195, 1925.

The ears of rabbits were painted with tar at intervals of a few days for seven months, and the resulting growths observed. Arsenic given internally and mechanical irritation seemed to favor their development. Nodules appeared in seventeen days, began to show characteristics of malignancy at the end of thirty days, but only after months became definitely malignant. The number, character, course and result of the growths varied greatly in different animals and even in the same animal. Some were histologically malignant, some were benign, resembling cutaneous horns, and some showed a tendency to recede. A certain, possibly transient, "predisposition to cancer" on the part of normal cells or cell groups is suggested by the authors as a possible cause for these differences.

B. R. LOVETT.

THE CYTOLYTIC ACTION OF SILENIUM AND ITS COMPOUNDS. A. H. ROFFO and L. M. CORREA, Bol. d. Inst. de med. exper. **1**:717, 1925.

The dissolving power of organic compounds of silenium on neoplastic cells was tested in vitro. By varying the cation, the toxicity of the compound could be reduced. The destruction of neoplastic cells was found to be much greater than that of normal cells.

B. R. LOVETT.

EPITHELIAL LESIONS PRODUCED BY PETROLEUM. A. H. ROFFO, Bol. d. Inst. de med. exper. **1**:735, 1925.

Prolonged chemical irritation with petroleum produced hyperkeratotic epithelial lesions. These were somewhat similar to the lesions produced by tar, but were more of the precancerous type, with less infiltration of the skin.

B. R. LOVETT.

CONCERNING BONE FORMATION IN A TUMOR OF THE HYPOPHYSEAL STALK. M. MEYER, Beitr. z. path. Anat. u. z. allg. Pathol. **73**:518, 1925.

An epithelial hypophysial duct tumor in a 12 year old girl was associated with calcification of the epithelial tissue and with true bone formation in the surrounding fibrous tissue. Meyer concludes that the tumor was not a teratoma.

O. T. SCHULTZ.

BLOOD GROUPS IN CANCER. G. WEITZNER, Med. Klin. **21**:1960, 1925.

Weitzner determined the blood group in eighty-four patients with carcinomas and in over 1,000 controls. The group percentage in cancer cases was: group 1 (Jansky) 16.6 per cent; group 2, 42.9 per cent; group 3, 14.3 per cent; group 4 (AB), 26.2 per cent. His controls were: 35.7 per cent, 43.3 per cent, 15.7 per cent and 5.3 per cent, respectively. He points to the distinctly smaller occurrence of the agglutinogens in cancer. Group 4 seems to indicate a predisposition, group 1 a resistance, to cancer.

Medicolegal Pathology

TRAUMA AND MALIGNANT TUMORS. CORDONNIER and MULLER, Ann. de méd. leg. **5**:226, 367, 1925.

An epithelioma developed in the nose where hot tar had accidentally lodged sixteen days previously, and two separate similar tumors in another laborer are attributed to wounds from ragged bits of briquettes of coal embedded, one in an eyelid, the other in the forehead.

In the discussion (Tenth Congress of legal medicine, Lille, 1925) considerable doubt was expressed regarding the propriety of ascribing the growths to single brief violent injuries, forms of trauma hitherto unassociated with carcinoma.

E. R. LECOUNT.

MEASUREMENT OF THE PUPIL IN DEAD BODIES. H. WILLER, Deutsch. Ztschr. f. d. ges. gerichtl. Med. **6**:22, 1925.

In spite of demonstrations twenty years ago by Placzek that the pupils contract regularly after death from a rigor in all particulars similar to that appearing in both smooth and skeletal muscles, statements are still made in standard textbooks of forensic medicine about the effect the mode of death, poisons and certain drugs and especially mydriatics given or applied before death, exert on postmortem appearances of the pupils. This is especially true as regards the alleged postmortem effects of atropine. It is true that postmortem rigor contracts the pupils more slowly if they are abnormally dilated before death and that one pupil markedly contracted before death enlarges to the size of the other before postmortem rigor effects contraction.

FORENSIC DEMONSTRATION OF POISON AFTER CREMATION. III. ORGAN STERILIZATION. FRITZ LIPPICH, Deutsch. Ztschr. f. d. ges. gerichtl. Med. **6**:268, 1925.

This third report by Lippich of carefully controlled experiments to render toxicologic methods more precise is concerned with demonstrating the value of sterilizing the stomach and its content for one hour at 100 C. so as to preserve organic poisons it may contain from decomposition they are likely to undergo when kept for some time.

Cocaine, chloroform, liquor formaldehydi, morphine, chloral hydrate, aconite, apomorphine, atropine and colchicine were used and the poisons recovered in from fifty-six to sixty days after the sterilization. No contamination with either aerobic or anaerobic bacteria was found.

Tables are given for the amounts of the respective poisons recovered, and the methods employed are described. The stomachs used were from medicolegal necropsies at the Institute for Legal Medicine in Prague, the causes for death being in no way connected with poisoning. Special apparatus to prevent the escape of volatile poisons had to be devised, and the results reported commend the methods.

E. R. LE COUNT.

Willer using a pupillometer, measuring to 0.1 mm. with precision, estimated the changes postmortem in thirty bodies at Danzig, and found that contraction begins in the pupils during the first hour or two after death, that the contractions first measured varied from 0.3 to 0.9 mm., and that contraction is not preceded, as some have asserted, by any preliminary dilatation. Intraocular tension which promptly disappears from normal eyes at the time of death and dehydration from unclosed lids after death produce minimal effects on the postmortem rigor contraction. Willer confirmed the observations by Marshall (1885) that atropine applied to the eyes after death retarded the rigor contraction of the pupils.

Many experiments with animals have been made and by a number of investigators, but it is clearly indicated that to settle definitely some of the debated questions, measurements as precise as those of Willer should be made of the iris rigor in death from various poisons and in persons with pupils greatly changed from disease or from drugs acting before death.

Like the old fictions concerning the heart stopping in systole, now largely replaced by studies of the postmortem rigor of cardiac muscle, inexact and even fantastic notions of the importance of the size of the pupils after death may give way to competent explanations of the rigor in the muscles of the iris and the conditions affecting its development.

E. R. Le Count.

Demonstration of Spermatozoa. B. Mueller, Deutsch. Ztschr. f. d. ges. gerichtl. Med. **6**:384, 1925.

The material stained with what is presumed to be seminal fluid is first cut up into fine particles and then macerated for twenty-four hours or longer in the cold to lessen the harm from bacterial growth. For the same purpose one part of a 1:1000 mercuric chloride solution may be used for every two parts of distilled water used for maceration.

After the soaking, the fluid is squeezed from the divided bits of fabric which are removed, and such fluid centrifuged with the rest, cover glass preparations made of the sediment and stained, preferably with the iron-hematoxylin method or some of its modifications.

By carefully controlled experiments Mueller found that spermatozoa could be demonstrated when other methods failed.

E. R. LeCount.

Technical

The Colloidal Benzoin Reaction in Acute Poliomyelitis. Joseph C. Regan, Am. J. Dis. Child. **30**:844, 1925.

In epidemic poliomyelitis and tuberculous meningitis the arachnoid fluid appears to react with colloidal benzoin in the meningitic zone, and this reaction may be of value in differentiating these diseases from epidemic encephalitis.

Dangers in the Use of Certain Halogenated Phthaleins as Functional Tests. W. H. Rosenau, J. A. M. A. **85**:2017, 1925.

Following the use of phenoltetrachlorphthalein, thromboses, local inflammatory reactions at the site of injection and chills have been encountered by many observers. Several deaths probably due to its use have been reported.

Clinical and experimental work indicates the possibility of strain or damage to the liver following injection of the dye.

Attempts to make phenoltetrachlorphthalein nonirritating on injection have failed.

Many observers have noticed severe toxic reactions following the use of tetra-bromphenolphthalein and tetra-iodophenolphthalein.

The toxicity of the halogenated phthalein compounds should lead to caution in their use. Indiscriminate administration and overdosage should be avoided.

AUTHOR'S SUMMARY.

THE REACTION OF SEDIMENTATION OF RED BLOOD CORPUSCLES IN PULMONARY TUBERCULOSIS, ITS DIAGNOSIS AND PROGNOSTIC VALUE. WILLY RACINE, Rev. méd. de la Suisse Rom. **45**:556, 1925.

A series of 406 sedimentation tests were made at intervals in 106 cases of pulmonary tuberculosis. Though the reaction is not specific, it is delicate and has a numerical value in the determination of the extent of a pathologic process and the character of the evolution of the lesion. Acceleration of the rate of sedimentation is a bad prognostic. The rate of sedimentation depends on the equilibrium existing between the forces of molecular attraction and the electrical repulsion of the red blood corpuscles, which have normally an electronegative charge. Fibrinogen in the blood is a measure of cellular destruction. In abnormal conditions the electropositive charged particles of fibrinogen and to some extent other globulins are absorbed by the corpuscles, and equilibrium is disturbed; the molecular forces act and rouleaux formation and sedimentation result.

G. B. RHODES.

A NEW LIVER-FUNCTION TEST. W. ARNOLDI, München. med. Wchnschr. **72**: 1414, 1925.

The test is based on determinations of the coloring matter (bilirubin) in the blood serum after oral administration of 20 Gm. of glucose.

ARTHUR LOCKE.

A NEW TITRIMETRIC PRINCIPLE AND ITS APPLICATION TO SUGAR AND URIC ACID DETERMINATION. L. FLATOW, München. med. Wchnschr. **72**:2009, 1925.

Potassium ferricyanide, a suitable agent for the oxidation of glucose or of uric acid, may be titrated quantitatively with sodium indigomonosulphonate. The intense blue color of this reagent is sufficiently visible when added in a two-thousandth normal dilution. Titrimetric methods are suggested for the determination of blood sugar and uric acid and of the uric acid in urine. Neither microburets nor precision readings are required. No protocols are included.

ARTHUR LOCKE.

THE PREPARATION OF OXYHEMOGLOBIN FROM HUMAN BLOOD AND ITS DETERMINATION IN ABSOLUTE AMOUNTS. W. AUTENRIETH and K. DORNER, München. med. Wchnschr. **72**:2043, 1925.

A method is given for the preparation of pure human oxyhemoglobin and for its use in the calibration of hemometers.

ARTHUR LOCKE.

THE RELATION OF THE ELECTRICAL CONDUCTANCE OF THE CEREBROSPINAL FLUID TO THE COLLOIDAL GOLD AND "AUROLUMBAL" REACTIONS. R. SCHAEFER, Klin. Wchnschr. **4**:2202, 1925.

The conductance of the cerebrospinal fluid varies from 0.0105 to 0.0200 mhos. These values seem to have no relation to the response to the Nonne, Pandy, Wassermann or colloidal gold reactions, nor to the cell count or pressure values.

ARTHUR LOCKE.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Jan. 11, 1926

RUTH TUNNICLIFF, M.D., *President, in the Chair*

DIABETES INSIPIDUS ASSOCIATED WITH SYPHILIS OF THE HYPOPHYSIS. DR. E. B. FINK.

This is a report of diabetes insipidus in a man, of twenty years' duration, beginning about five years after a primary syphilitic lesion with symptoms of syphilitic meningitis. At first the polydipsia was extreme and the polyuria enormous. Both improved temporarily under antisyphilitic treatment and were partially controlled by hypodermic injections of pituitrin. Signs of hypophysis dystrophy developed, consisting of loss of body hair, moderate adiposity and atrophy of the genitals. During the few months before death the diabetes insipidus had apparently disappeared.

At necropsy, the changes of interest concerned the hypophysis. It was extremely small, a disk 11 mm. transversely, 7 mm. vertically, and 0.5 mm. thick, including the thickened capsule, which was not to be differentiated from the thickened dura with which it merged. There was no distinct hypophysis, and its location was determined solely by the entrance of the infundibulum into the thickened fibrous tissue. Microscopically, the infundibulum, posterior lobe and pars intermedia were replaced by dense avascular scar tissue. No remains of the anterior lobe were found except in the middle of the mass, where there was glandular tissue about 2 mm. in diameter.

The base of the brain was divided into four blocks, embedded in paraffin and cut in series. The ganglion cells scattered through the hypothalamus and in the tuber cinereum were normal. Nowhere was there round cell infiltration.

In our conception of the pathogenesis of diabetes insipidus, cases in which the lesion is confined to the posterior lobe and infundibulum of the hypophysis cannot be ignored. The hypophysis and midbrain are anatomically united, and in all probability this is true of their function. A lesion in any part of this unit may result in diabetes insipidus, although not invariably. It is just as inconsistent with the facts to state that the hypophysis bears no relation to diabetes insipidus as it is to deny that lesions of the tuber cinereum produce it.

THE INFLUENCE OF DIFFERENT FORMS OF DIET ON THE EXPERIMENTAL AMYLOIDOSIS IN MICE. DR. R. H. JAFFÉ.

Feeding cholesterol and fat or dried beef heart powder increases the resistance of mice against the toxic action of long continued injections of foreign proteins. Thus, the formation of amyloid can be delayed for a considerable length of time. The fat diet, however, is effective only when started together with the injections. If there is an interval between them, the beginning of the injections preceding the diet for more than two weeks, no protection of the mice is noted. The experiments with cholesterol reveal an alterated cellular activity of the liver which precedes immediately the onset of the amyloid changes. This is manifested by a marked reduction in the ability

of the liver cells to store the cholesterol as double refractive droplets and crystals. The differences between the effect of feeding cheese and beef heart powder is explained on the basis that cheese causes a chronic irritation of the intestine and thus may lead to amyloidosis while the beef heart is a more suitable form of protein diet, does not affect the intestinal mucosa, and may even prevent amyloid degeneration.

The complete article is published in Arch. Path. **1**:20, 1926.

AN EXPERIMENTAL METHOD FOR THE STUDY OF THE BACTERIAL FLORA AND THE HYDROGEN-ION CONCENTRATION OF THE GASTRO-INTESTINAL TRACT. DR. LLOYD ARNOLD.

A method was devised for fixing certain segments of the intestinal tract to the anterior abdominal wall in such a way that the content of a particular segment could be aspirated for chemical and bacteriologic study. The duodenum was found to contain relatively few bacteria; the H-ion concentration varied from p_H 5.2 to 6.2. The upper part of the jejunum contained the same bacterial flora; the H-ion concentration was a little more alkaline—p_H 5.5 to 6.6. The lower jejunum was found to contain a richer bacterial flora, the gram-negative bacilli were usually encountered in the region, and the H-ion concentration approached neutrality. The ileum had a mixed bacterial flora, similar to that found in the feces; the H-ion concentration was neutral or slightly alkaline.

When alkaline, buffered salt solution (p_H 8-9) is injected into the duodenum, and the bacterial flora changes to the type usually found in the ileum. Acid buffered solutions do not change the bacterial flora. When the gastric acidity was depressed by the elevation of the temperature, the duodenal bacterial flora was found to be fecal in type.

A peripheral leukocytosis was associated with an alkalinization of the duodenum. The maintenance of the normal H-ion concentration and the normal bacterial flora of the content of the duodenum and upper jejunum are dependent to a great extent on the normal gastric secretion.

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, Jan. 14, 1926

E. B. KRUMBHAAR, M.D., *President*

A RARE TYPE OF PATENT DUCTUS ARTERIOSUS. ARTHUR D. WALTZ. (From the Laboratory of the Children's Hospital, Philadelphia.)

The specimen was from a white girl, 7 months old. Significant features of the clinical record were marked enlargement of the heart, chiefly to the left, with a soft blowing systolic murmur over the entire chest anteriorly and on the left side posteriorly. Roentgen-ray examination showed marked widening of the right auricle, left ventricle and pulmonary arch, a combination strongly suggesting a patent ductus Botalli.

This specimen was presented not because patent ductus arteriosus Botalli is in itself a rare condition, but because this particular type is rare as reported in the literature.

Quoting from Dr. Maude Abbott: "There are two types. In the common type the ductus persists as a short canal ranging from 0.4 to 2 cm. in length,

running from the left branch of the pulmonary artery directly after the bifurcation to the under side of the arch of the aorta just beyond the origin of the left subclavian artery. In rare cases the duct may be greatly shortened on itself so that its ends are approximated to each other, and it disappears as a canal, remaining an aperture between the two great trunks."

The specimen presented belongs to the latter class. The arch of the aorta just beyond the origin of the left subclavian artery touches the pulmonary artery at the point of bifurcation, and they communicate with each other at this point by a circular opening 0.6 cm. in diameter. The heart shows a general hypertrophy, which seems if anything slightly more marked on the right side, and the pulmonary artery is relatively large in comparison to the aorta.

TUBERCULOSIS OF THE MYOCARDIUM WITH ASSOCIATED MILIARY TUBERCULOSIS. JOHN T. BAUER. (From the Ayer Clinical Laboratory, Pennsylvania Hospital.)

A colored youth, aged 19, was admitted to the Pennsylvania Hospital in June, 1925, with the complaint of pain in the right side. His health had been good until six months previously, when he felt run down and was compelled to stop work. In addition to the pain in the region of the right hip, there was a history of recent loss of weight, occasional precordial pain, night sweats and expectoration. On examination it was found that the relative cardiac dulness was increased but shifted with change of position. The heart sounds were muffled, and a short systolic murmur was audible at the apex. The remainder of the examination revealed no contributory data. The history and physical findings suggested incipient tuberculosis with early pericarditis and auricular fibrillation. Roentgenologic studies of the thorax and spine at this time revealed nothing noteworthy except a greatly enlarged heart. The patient remained but a short time in the hospital only to return in October, 1925, complaining of dyspnea of two months' duration. At this time there were evidences of cardiac failure, pretibial edema, ascites, an enlarged, firm and tender liver, hypotension and pulmonary edema. Cardiac findings were unchanged. Adhesive tuberculous pericarditis was considered the most likely clinical diagnosis. This view was further emphasized by the roentgenologic findings which suggested miliary tuberculosis, and erosion of the first lumbar vertebra which had not been present three months previously. His condition gradually grew worse, and he died on Nov. 3, 1925.

At necropsy the body showed marked emaciation. Miliary tubercles were scattered throughout the omentum and peritoneum, and studded the surface of the abdominal and thoracic viscera. There was a psoas abscess on the right side, which had its origin in the first lumbar vertebra and extended to the adjacent vertebrae. The lungs were firm and studded with miliary tubercles. No old pulmonary focus was noted. The tracheobronchial lymph glands were enlarged and caseous but not calcified.

The pericardial cavity was obliterated by fibrous and caseous tissue which covered the heart as far as the base of the great vessels. No fixation of the heart against the chest wall was noted. An active tuberculous process seemed to begin in the pericardium and extended downward into the thickened myocardium particularly involving the walls of the left ventricle. Here much of the muscle was destroyed, and caseation penetrated at places to the endocardium. Caseous areas were most numerous over the endocardial surface of the right auricle distal to the valvular orifices, but the other chambers were also involved. The valves were competent and not affected.

The degree of myocardial destruction was further emphasized by the sections which showed large tubercles extending well between the muscle fibers and destroying them.

Cardiac muscle is seldom involved except in miliary tuberculosis, and then generally only a few scattered tubercles are present. Fibrinous tuberculous pericarditis is more frequent, but caseous involvement of pericardium and myocardium seldom takes place except by direct extension from tuberculous mediastinitis.

That such an extensive lesion should be present in the heart as exists in this case is significant as only one similar case was found in the necropsy series at the Ayer Laboratory (covering 3,100 necropsies), although similar cases have been presented before the Pathological Society in the past.

This case is unusual because it appears that the pericardium and heart muscle were the oldest and most advanced lesions present; secondly, it raises the question as to whether the heart may not have been the point of miliary dissemination.

THE ORIGIN AND DEVELOPMENT OF MONOCYTES IN MONOCYTIC LEUKEMIA. MAURICE N. RICHTER.

The origin and development of monocytes (large mononuclear and transitional leukocytes) are less well known than in the case of most other blood cells. Favorable opportunities for studying the developmental stages of these cells are afforded by cases of monocytic leukemia, in which immature monocytes (monoblasts) may appear in the circulation in large numbers.

In two cases of monocytic leukemia recently observed, it was possible to trace accurately the development of monocytes. They arose by differentiation of a primitive blood cell morphologically identical with the "hemocytoblast" of Ferrata or the "myeloblast" of Naegeli.

The first recognizable stage of their differentiation was the appearance of azurophilic granules in the cytoplasm. Development proceeded by increase in the number of granules, and by change of the nuclear shape and structure from that of the hemocytoblast to that of the monocyte.

As azurophilic granules occur in lymphocytes, platelets and megakaryocytes, and immature myeloid cells as well as in monocytes, it is necessary to study the properties of these granules in greater detail. Although differences among azurophilic granules have been described, suitable criteria for their systematic classification are lacking.

By the use of other stains than the usual blood stains, differences among azurophilic granules may be demonstrated. Thus the granules in myeloid cells and mature monocytes react positively to the benzidine peroxydase solution; those of lymphocytes, platelets and immature monocytes do not; the granules of myeloid cells and platelets are demonstrable by the phenyl toluidin blue method of Sabrazes; those of lymphocytes and monocytes are not. These reactions enable us to distinguish four varieties of azurophilic granules, which may be designated by the name of the cell in which they occur, namely: lymphocytic, monocytic, myeloblastic and platelet-megakaryocytic varieties.

In the cases here reported, the granules reacted in the manner of monocytic and monoblastic azurophil granules.

Theories of the origin of monocytes under normal conditions form the basis of the several views regarding the pathogenesis of monocytic leukemia. In some of the reported cases, the reticulo-endothelial system has been thought to be the main source of monocytes. In the cases here reported, the reticulo-

endothelium played but little part in blood formation, the monocytes being derived from blood stem cells or hemocytoblasts. As monocytes may have other origins as well as the one described, the hemocytogenic activities of the connective tissues may be more manifest in some cases than in others.

The hemocytoblasts which gave rise to the monocytes in these cases were apparently identical with those which, under other conditions, give rise to other varieties of blood cells. This fact favors the view that the hemocytoblasts are not specific, but indifferent, polyvalent cells.

FUNCTIONS OF THE SPLEEN. E. B. KRUMBHAAR.

The mammalian spleen, while not necessary for the maintenance of normal existence and sharing many functions with other members of the hemolyto-poietic system, is useful in several ways, and it is an organ whose presence under certain stresses may even be the deciding factor between life and death. Its functions are largely indicated by its structure, reticulo-endothelial cell content and by the changes produced in other organs by its absence.

There is good reason to consider it a blood reservoir that can be called on to meet efficiently various physiologic and pathologic demands.

It is directly concerned in blood cell formation during fetal life and can revert to this function on demand at any period of existence. It continues to furnish lymphocytes, large mononuclears and possibly other blood cells through most of adult life and has an indirect influence on blood formation through stimulating action on the bone marrow, possibly after activation by the liver.

It is intimately concerned in the processes of red blood cell destruction, a rôle greatly increased in certain pathologic conditions. It not only, in some way as yet unknown, renders circulating erythrocytes more fragile, but through its reticulo-endothelial cells has the ability to scavenge blood cells and bacteria from the blood. It takes up disintegrating erythrocytes as a step in blood pigment metabolism, either in the form of fragmented cells, hemoglobin-bearing dust or even, in conditions of increased hemolysis, of whole cells (graveyard function). It not only is the richest hoarder of iron in the body, but also prepares bilirubin pigment from the broken-down hemoglobin for passage to the liver. In the absence of the spleen it becomes more difficult to produce jaundice with hemolytic agents. Continental authorities consider it the controlling organ of iron metabolism in the body.

It seems to be an important site of antibody formation (again through the reticulo-endothelial cells), though this function is quickly taken up by other organs in its absence. Through its lymphoid rôle, it also plays a part in resistance to such infections as tuberculosis. Preponderating evidence points to its also being concerned with biologic resistance to tumor growth.

Its relation to metabolism is less manifest. Disturbances in growth and digestion following its removal maintained by some are denied by more, and the same can be said of its relation to basal, nitrogen and carbohydrate metabolism. It seems to have a more definite connection with fat metabolism, especially cholesterin and the unsaturated fatty acids, which may be the reason for the improvement which splenectomy often procures in clinical anemias, though here, too, authorities are far from unanimous.

With regard to its relations to other organs, the liver, lymph nodes (lymphoid tissue generally) and bone marrow, as members of the hemolyto-poietic system they are so closely allied that they share certain functions normally and quickly take them over after extirpation of the spleen. It has special affiliations with

the liver on account of its definite "upstream" position in the portal circulation and possibly others of a more specific incretory nature. Supposed antagonistic relations with the thyroid await confirmation; a connection with the thymus apparently does not exist, and a possible synergistic relation to the pancreas is probably better explained as an especially marked participation (perhaps through its reservoir function) in the effects of inanition, rather than by a specific hormonal connection.

Book Reviews

DEVELOPMENT OF OUR KNOWLEDGE OF TUBERCULOSIS. By LAWRENCE F. FLICK, M.D., LL.D. Cloth. Price, $7.50. Pp. 783. Philadelphia: The Author, 1925.

This volume is a source book with extensive readings from the classics of literature on tuberculosis. In it we find arranged in chronologic order excerpts from the most famous treatises on this disease from Hippocrates to the Sixth International Congress on Tuberculosis in Washington, in 1908. The book is well indexed and valuable for the ready access which it furnishes to these. The author submerges his own personality, and for the most part attempts only to direct the reader's attention to certain selections, for which he furnishes the headlines and brief editorial introduction. The great length of the quotations from the classics robs the book of some of the dramatic interest which might be expected in a history of tuberculosis. On the other hand, should the reader wish to compare the views of Hippocrates, Galen and Araeteus, Morton and Matthew Baillie, Laennec, Virchow and Villemin, or any of the other early writers of note, he may feel assured that the author has not failed to include, in the original or in careful translation, their outstanding contributions on the subject. Seventy pages are devoted to the "Phthisiologia" of Morton, and 120 to the studies of Villemin, mostly in the form of direct quotation. Koch's original article on the tubercle bacillus is reproduced almost in entirety, translated into English. One of the most interesting parts of the book is an analysis of the now almost forgotten claims of Aufrecht and Baumgarten for priority in the discovery of the bacillus. In stopping with the opening of the twentieth century, Dr. Flick fails to include the clinical use of the roentgen rays, our present knowledge of the extent of tuberculous infection, and our recognition of the hypersensitive state in tuberculosis. A consideration of these would round the book out, without passing the limits of our "knowledge" of tuberculosis. This omission is, however, deliberate, as the author feels that the first quarter of the twentieth century would require a volume for itself.

CLINICAL LABORATORY MEDICINE. A TEXTBOOK OF CLINICAL, LABORATORY, DIAGNOSTIC AND THERAPEUTIC PROCEDURES, by HENRY M. FEINBLATT, M.D., and ARNOLD H. EGGERTH, A.B., A.M. Illustrated by two color plates and eighty-seven engravings. Price $5.00. Pp. 424. New York: William Wood and Company, 1925.

This laboratory text has thirty-two chapters containing directions for the examination of various fluids or tissues of the body and for determining the function of certain organs. Sufficient detail is given with the instructions to make them easily followed. Together, the chapters cover fully the technic of routine clinical laboratory examinations. Distinctive is the summary given with each test which mentions the normal value, the clinical significance of a result differing from the normal and the diseases in which changes from the normal occur. There may be objection to some of the interpretations given, but in general they are conservative. This book is helpful to the laboratory worker in making tests, and to the clinician as a guide in understanding the results obtained.

THE PATHOLOGY OF TUMORS. By E. H. KETTLE, M.D., B.S. (LOND.), Professor of Pathology and Bacteriology, Welsh National School of Medicine, Cardiff; Formerly Pathologist and Lecturer on General and Special Pathology, St. Mary's Hospital and Medical School; Pathologist to the Cancer Hospital, Brompton. Second edition. Price $5. Pp. 285, with 159 illustrations. New York: Paul B. Hoeber, Inc.

The book presents succinctly the current teachings in regard to the biology and structure of tumors. On account of brevity, the part dealing with the tumors of special tissues and organs is in essence merely an enumeration or catalog. With two or three exceptions, the illustrations are excellent. Nothing seems to be said of the part hereditary factors play in cancer. Benign giant cell sarcoma is discussed under myeloid sarcoma. It is of interest to note that examples are cited of cancers developing in a short time — from two to six weeks — on burns by hot tar. On the whole, the book gives in condensed form a reliable summary of our knowledge of tumors.

A TEXTBOOK OF PATHOLOGY. GENERAL AND SPECIAL. By J. MARTIN BEATTIE, Professor of Bacteriology, University of Liverpool, and W. E. CARNEGIE DICKSON. Third edition. Cloth. Price, $11.00. Pp. 1103, with 499 illustrations and 17 colored plates. St. Louis: C. V. Mosby Company, 1925.

In this edition the two parts, on general and special pathology, are included in one volume. This book is based on the teachings of the Edinburgh school, designed for medical students and practitioners, presented in easily read print freely accentuated with heavy type and italics, and abounds in illustrations. The chapter on animal parasites appears with perhaps more than ordinary length, while some special subjects, such as bacteriology, because of more adequate treatment in separate textbooks, have been omitted or are only briefly mentioned. Little attempt is made to include chemical pathology, although the recent work on insulin is reviewed. It appears to be a reliable book for practical use.

ACUTE INFECTIOUS DISEASES. A HANDBOOK FOR PRACTITIONERS AND STUDENTS. By J. D. ROLLESTON, M.A., M.D. (OXON), Senior Assistant Medical Officer, Grove Fever Hospital, London; Editor, British Journal of Children's Diseases; President, Section of History of Medicine, Royal Society of Medicine. Price $5. Pp. 376. New York: Physicians and Surgeons Book Company, 1925.

Dr. Rolleston has written clear and brief accounts of the chief acute infectious diseases, those ordinarily treated in isolation hospitals. Typhoid and typhus fevers are included, but poliomyelitis, encephalitis and others are not. The clinical aspects, symptoms and treatment are given fully, the etiology and morbid changes more briefly. Some of the recent advances in the field are discussed, such as the prevention of measles with convalescent blood and serum, although there is no mention of the treatment of scarlet fever with antitoxin. The historical notes at the beginning of each chapter are interesting, and the bibliographic notes at the end are helpful in further reading on the various subjects.

CHEMICAL PATHOLOGY. By H. GIDEON WELLS, PH.D., M.D. Fifth edition, revised and reset. Pp. 790. Philadelphia: W. B. Saunders Company, 1925.

There are a few books in almost every field of modern science which promptly claim widespread recognition from the students of the subject. This

may be because the writer has attempted new, compelling generalizations that are destined to modify profoundly the development of the theme under discussion; or the contribution may present familiar topics with skill in arrangement, with clarity in exposition, and with a wealth of pertinent illustrations that constitute a masterful scientific story. Occasionally such books command large groups of interested readers, though they usually have a comparatively short period of such enthusiastic reception. The strides of experimental science are rapid, so that the novelty of today becomes antiquated tomorrow. It is more rarely that a treatise is kept so effectively up to date that its prestige is retained beyond the usual brief life of a textbook.

The demonstrated popularity of Wells' "Chemical Pathology" throughout nearly two decades replete with rapidly changing views and achievements, particularly in biochemical research, is a tribute of no mean order. The book has become a vade mecum for many investigators. It indicates the growing possibilities of chemical procedures in medical research, particularly in the domain of pathology; and the uncertainties of present-day achievement are sufficiently indicated to point the way to possibilities of further endeavor and progress.

As a single illustration of the varied points of view from which the author has examined his themes the chapter on edema may be cited. Physiology, physical chemistry and pathology are invaded to bring out their respective offerings to the difficult problems of genesis. The formation and movement of lymph are considered as an appropriate introduction to the subject; and when the reader approaches the "summary" he is conscious of something other than a dogmatic review of the subject. Then follow the detailed considerations of the varied possible pathogenetic factors in edema, presented with historical perspective as well as current timeliness. There are discussions of the special clinical manifestations of edema dependent on unusual causes; of the analytic and physical chemistry of edematous fluids, etc. Every chapter is a record of evidence which the trained mind may use to advantage.

The comparison of the five successive editions will serve as an indication of scientific progress in a multitude of departments since 1907. Some of the outlying "novelties" of the earlier editions are now omitted because they have become permanently entwined in the fabric of biochemical knowledge. The elaborate system of footnote references makes the book cyclopedic without destroying its readability. Few investigators of the present period of intense specialization are competent to attempt a comprehensive presentation of a "borderline science" such as chemical pathology touching on many fields represents. The author deserves the compliment that the continued cordial reception of his book implies; perhaps it is not presumptuous to intimate the hope that having sustained his mastery for many years he may be able to continue in his "path of helpful endeavor" when the need of another revised edition becomes apparent.